IntechOpen

# Current Topics in Intensive Care Medicine

*Edited by Rıza Hakan Erbay*

# CURRENT TOPICS IN INTENSIVE CARE MEDICINE

Edited by **Rıza Hakan Erbay**

**Current Topics in Intensive Care Medicine**
http://dx.doi.org/10.5772/intechopen.73143
Edited by Rıza Hakan Erbay

**Contributors**

Nandita Mehta, Sayyidah Aasima Tu Nisa Qazi, Dyah Wati, Delia Muntean, Monica Licker, Bogdan Pavel, María Ángeles Rosero Arenas, Alfonso Martínez Cornejo, Miguel Ángel García García, David Arizo León, Jae Kim, Nikolai Shalygin, Azif Safarulla

**Notice**

Statements and opinions expressed in the chapters are these of the individual contributors and not necessarily those of the editors or publisher. No responsibility is accepted for the accuracy of information contained in the published chapters. The publisher assumes no responsibility for any damage or injury to persons or property arising out of the use of any materials, instructions, methods or ideas contained in the book.

# We are IntechOpen,
# the world's leading publisher of Open Access books
# Built by scientists, for scientists

## 3,700+
Open access books available

## 115,000+
International authors and editors

## 119M+
Downloads

## 151
Countries delivered to

Our authors are among the
## Top 1%
most cited scientists

## 12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS

**BOOK CITATION INDEX**

INDEXED

**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

# Interested in publishing with us?
# Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

# Meet the editor

Dr. Riza Hakan Erbay was an anesthesiologist at the Pamukkale University in 1996. He worked as an assistant professor in 1997, an associate professor in 2005, and a professor in 2011. He has mainly worked in the field of orthopedic anesthesia, regional anesthesia, and intensive care medicine. He worked as an education coordinator at the Faculty of Medicine during 2007–2009. He served as the vice president of Surgical Sciences Department, Faculty of Medicine, during 2009–2012. He was an intensivist in 2013. He worked as the head of the Anesthesiology Clinic at the Izmir Tepecik Training and Research Hospital during 2013–2014. He is currently the chairman of the Department of Anesthesiology and Reanimation at the Faculty of Medicine, Pamukkale University.

# Contents

# Preface

Intensive care medicine is rapidly evolving and becomes increasingly complex, and the basic and clinical skills required to treat critical illnesses continue to transcend subspecialties. For this reason, intensivists have to master a number of medical disciplines such as anesthesiology, surgery, chest diseases, psychiatry, and infectious diseases. In this book, critical care for neonatal, neurological, and cardiological patients; fluid management in these patients; and intensive care infections are included. We hope the readers find this book to be helpful.

**Prof. Dr. Riza Hakan Erbay, M.D.**
Chairman of Department of Anesthesiology and Reanimation
Faculty of Medicine
Pamukkale University
Denizli, Turkey

# Fluid Management in ICU

# Measuring and Managing Fluid Overload in Pediatric Intensive Care Unit

Dyah Kanya Wati

Additional information is available at the end of the chapter

**Abstract**

Fluid management is one of the regular aspects of care in pediatric intensive care unit (PICU) setting, and its importance has been stressed in previous studies. Fluid resuscitation, as part of fluid management, may be needed to maintain intravascular volume, and prior studies showed that early aggressive fluid resuscitation may improve outcome in critical illness, especially in endothelial-dysfunction associated conditions. Unfortunately, this routine management often leads to the development of positive fluid balance and, consequently, fluid overload. Many evidences have stated that excessive fluid administration is closely associated with negative effects for children who were admitted in PICU. Moreover, fluid balance before PICU admission is also important because uncertainty about quantification fluid balance before admission can lead to underestimated fluid overload.

**Keywords:** positive fluid balance, children, pediatric intensive care, managing

## 1. Introduction

Fluid management is one of the regular aspects of care in PICU setting, and its importance has been stressed in previous studies [1]. Fluid resuscitation, as part of fluid management, may be needed to maintain intravascular volume [2], and prior studies showed that early aggressive fluid resuscitation may improve outcome in critical illness [1], especially in endothelial-dysfunction associated conditions [3]. Unfortunately, this routine management often leads to the development positive fluid balance and consequently, fluid overload (FO) [1, 3, 4]. Many evidences have stated that excessive fluid administration is closely associated with negative effects for children who were admitted in PICU [3, 4]. FO was known to cause

increased risk of morbidity, mortality, additional time of mechanical ventilation, additional hospitalization time, and increased need for renal replacement therapy (RRT) [5, 6].

In patients who already have critically ill also shown that fluid overload shows a negative effect. Flori et al. [2] conducted post-hoc study about the association positive fluid balance with worse clinical outcomes in children with ALI. This study showed the increment of 10 mL/kg/day fluid balance was associated with increasing mortality. Moreover, the increments were also associated with fewer ventilator-free days. Flori also suggested that fluid overload itself may be a risk factor for mortality regardless of initial presenting severity of illness [2]. In another study involving 778 patients with septic shock post resuscitation also found that fluid overload increased up to twice the mortality rate [5]. Vincent et al. [7] in their research on sepsis patients found that each addition of a positive fluid balance after 72 h was associated with an increased odds ratio of mortality by 10%. Sutawan et al. [6] study also found that fluid overload was associated with mortality (OR 11.5; 95% CI: 3.7–35.6; p < 0.001) with a range of 12.9 ± 7.9% on 120 subjects.

## 2. Pathophysiology and measuring fluid overload

In general, the vascular endothelial allows free exchange of water, electrolyte, glucose, and nutrients components into and out of the tissue independently because of their permeability to the components. This transcapillary component exchange capability is affected by factors such as hydrostatic pressure, endothelial tone, and oncotic pressure. The fluid passing through the intact endothelial barrier and going to the extravascular generally will be reabsorbed by the lymphatic system to reduce edema. However, damage of endothelial barrier caused by the inflammatory process and edema will be easier to occur. The endothelial barrier is commonly known as glycocalyx, a network-rich carbohydrate and protein bond that regulates the process of exchanging fluid to extravascular (**Figure 1**) [8].

Beside its own endothelial tissue structure, intravascular volume stability is also regulated by baroreceptors located in the carotid, atrial, and afferent renal arterioles. The renin-angiotensin-aldosterone system (RAAS) will be readily activated resulting in natriuretic peptide secretion in the event of intravascular volume changes [10]. Activation of the RAAS system and the secretion of natriuretic peptides make water and sodium retained by the kidneys to maintain intravascular volume. Imbalance between intravascular and extravascular fluid or component like natrium will facilitate intravascular fluid to the interstitial so that edema, ascites, pleural effusion may occur. Some studies use FO percentage (FO%) as a tool to estimate the amount of fluid retention [9, 10].

$$\text{FO \%} = \left[(\text{fluid administrated} - \text{fluid eliminated}/\text{body weight when first arrived}\right] \times 100 \quad (1)$$

The fluids are measured in liters while the body weight measured in kilogram. FO% ≥ 10% is associated with high morbidity rates, such as worsening oxygenation levels, longer mechanic ventilator usage time, increased risk of renal replacement therapy (RRT), even to an increase
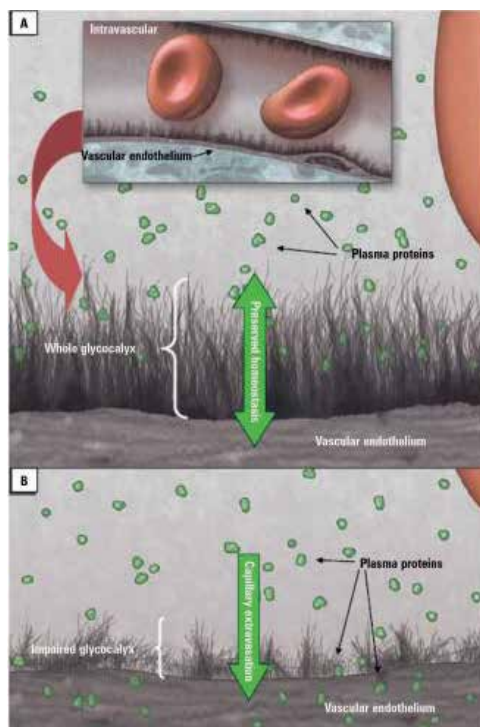
**Figure 1.** Schematic representation of glycocalyx [8].

in mortality. Patients who received RRT increased by 25% in critically ill patients. One of the risk factors is an increase in FO% levels between 10 and 20% [1, 11]. Similarly, in patients with ARDS, it is known that fluid retention increases mortality. Fluid overload with edema and extravasation manifestations into the third cavity is associated with failure of several systems such as the cardiovascular system, central nervous system, hepatic system, and digestive systems that stimulate malabsorption of nutrients and malnutrition in children. Fluid management for each critical illness in children is not the same depending on the clinical condition of the patient, but patients with high levels of FO% more frequently can cause failure of several organs [1–3, 12].

## 3. Pathophysiology fluid overload in sepsis and ARDS

In ARDS patients, some theories suggest that fluid overload can aggravate the patient's condition. Widespread injury of both lung and systemic endothelium with a resultant increase in permeability and expression of adhesion molecule is characteristic of ARDS/ALI [13]. Injury to the microvascular endothelium of the lung was first known almost 30 years ago [14, 15]. A variety of circulating markers of endothelial cell injury and activation have been studied in patients with ARDS/ALI. Endothelin-1, a vasoconstrictor and proinflammatory peptide is

released by endothelial cell as a result of injury, is increased in the plasma of patients with ARDS/ALI as is von Willebrand factor (VWF) antigen, another marker of endothelial cell activation and injury [13, 16]. Higher levels of plasma VWF were independently associated with mortality by multivariate analysis in two independent studies. Although injury to the lung microvascular endothelial is the underlying cause of increased permeability pulmonary edema in ARDS/ALI, endothelial injury and activation may also lead to obstruction or destruction of the lung microvascular bed in ARDS/ALI case [15]. The degree of obstruction and destruction of the lung microvascular bed is an important determinant of outcome and can be estimated by the pulmonary dead space fraction [1, 15].

Fluid management in sepsis patients is necessary to increase the perfusion of vital organs in order to restore the patient's hemodynamics. However, there has been no research suggesting the amount of fluid dosage in sepsis patients. Based on early goal directed therapy (EGDT) for the treatment of severe sepsis and septic shock, targeted fluid therapy used central venous pressure (CVP) [7, 17]. However, the target cvp is 8–12 mmHg to ensure intravascular volume. However, the EGDT guidelines do not limit the extent to which these fluids should be administered to patients. Even some recent studies suggest that fluid administration according to the EGDT concept has been abandoned because it is more likely to make hypervolemia and increase mortality rates in the first 48, 72, and 96 h post-EGDT [17]. This increase in mortality rates is more likely to be caused by FO, as FO may aggravate capillary leakage and contribute to or worsen edema in patients' lung with sepsis and septic shock. FO can also create intraabdominal hypertension, leading to organ hypoperfusion that will eventually fall on organ failure [18].

## 4. Managing fluid overload

### 4.1. Composition of resuscitation fluids

There is no ideal fluid used for resuscitation of shock patients. At least the fluid used has a similar chemical composition to the plasma and can eliminate shock signals without adding fluid extravasation to the interstitial cavity. Currently, the fluid used is colloidal fluid and crystalloid fluid [19].

Crystalloids are more recommended as first-line therapy to restore hemodynamics in patients with shock [20]. Crystalloids are made up of ions with various tonicities and can be freely distributed. The saline liquor is more isotonic to the plasma but has a higher concentration of chloride and is more at risk of hyperchloremic metabolic acidosis and increases the risk of kidney failure [18]. The fluid such as the ringer is more hypotonic than the extracellular fluid and is also associated with hyperchloremia but has a pH that is more similar to plasma pH [19–21].

Colloid is a fluid containing macromolecules with the usefulness of increasing the oncotic pressure and maintaining the amount of fluid that already exists in the vascular and even absorb fluid in extracellular to intracellular [5, 8]. Colloids are classified according to natural

(albumin) and artificial (gelatin, dextran, and hydroxyethyl starch (HES)) [7]. In contrast to the crystalloid fluid distributed among compartments, the colloidal fluid will remain in the vascular cavity for more than 16 h [8].

Gelatins, a polypeptide derived from collagen bovine, have the same extravascular extension as albumin but are associated with the risk of renal damage. HES is a high-molecular weight synthetic polymer and is associated with high incidence of renal failure and coagulation disease [8].

A study comparing the effects of crystalloid with HES found that the use of HES could reduce the amount of fluid intake (30% less than crystalloid), increasing CVP faster, decreasing the incidence of shock but increasing chances for RRT and increasing mortality [22].

## 4.2. Volume resuscitation

The resuscitation phase aims to restore intravascular volume, increase blood pressure, increase urine output, restore peripheral perfusion and increase consciousness level [17]. Aggressive fluid administration in this phase is associated with fluid overload [21]. The amount of fluid required in this phase also varies and depends on the individual patient [23]. Fluid management without adequate monitoring can increase the risk of volume overload [21]. Management using a vasopressor need not be delayed and aims to restore and maintain renal perfusion, optimize diuresis, and prevent fluid accumulation [10].

Predicting fluid delivery can reduce the risk of over-giving and unnecessary fluid [24]. Monitoring cardiac output and evaluation of vena cava diameter with ultrasound is one of the mechanisms used to monitor the amount of incoming fluid [25]. This method still has limitations due to the varied reference values that are used to assess the clinical patient, as each individual differs in the amount of fluid that enters depending on body weight, renal ability, and type of illness being suffered [26]. Some of these hemodynamic variables cannot be adequately calculated in patients with inadequate ventilation and receive low tidal volume. In the case of unstable hemodynamics, relative hypovolemia may occur due to the administration of sedative drugs or infectious processes [27].

Calculating central venous saturation and CVP does not show high sensitivity and specificity to predict fluid response [21]. It is estimated that more than 50% of patients are admitted to the ICU because of sepsis and do not respond adequately to this volume test [28]. Signs of tissue hypoperfusion such as lactate and central venous saturation are generally used to evaluate the appropriate time to stop fluid resuscitation [29]. A retrospective study of 405 septic patients receiving therapy based on the central venous saturation target and mean arterial pressure (MAP) protocols indicated a high risk of FO and mortality [30]. However, regular evaluation of venous saturation to evaluate resuscitation responses is more commonly used and is associated with fluid overload [31].

## 4.3. Maintenance volume

In patients with critical illness and treated in the ICU, FO should be avoided [23]. Treatment of fluid administration depends on each individual in the resuscitation phase. As described

earlier, FO is associated with high morbidity and mortality [28]. After returning blood pressure or on children returning heart rate is more valuable, the primary focus is adequate oxygen delivery to the tissue, which is directly related to cardiac output, hemoglobin concentration, and arterial saturation [32].

Conservative fluid management is associated with increased oxygen levels, decreased ventilator usage time, and decreased hospitalization. Patients treated in the ICU room on average will get fluid overload problems. Beside direct administration of fluids through venous access, these patients also receive fluids through drug administration and nutrient feeding and thus increasing the risk of fluid overload. However, in the maintenance phase, it is important to minimize the administration of unnecessary fluids [1, 33]. When FO is identified in a patient with stable hemodynamic and vasopressor reduction, fluid reduction should be the primary target to avoid negative FO effects [32].

### 4.4. How to monitor fluid overload in our patients?

Conventional indicators, such as MAP, pulse, weight, peripheral edema, are not reliably used in patients with critical illness. MAP and pulse rate are highly fluctuative due to drug use. Indicators of fluid volume such as end-diastolic volume and intrathoracic volume may be useful but still require further study for clinical validation. Cardiac index monitoring and ejection fractions can be used to diagnose FO. In patients with mechanical ventilation, the absence of variation in pulse pressure may indicate the presence of FO [10].

A study of 49 patients using Doppler crosslinks could predict better diuresis using the index compared with changes in pulse pressure and increased MAP after fluid administration. This suggests that renal hemodynamic enhancement is essential for the occurrence of urinary output and reduces FO [34].

In sepsis patient with hypotension, the renal autoregulation mechanism is damaged by microcirculation changes. In this phase, vasopressor administration is often used to keep renal perfusion adequate, and a diuretic process still exists. Research in adults who analyzed the use of noradrenaline to keep MAP between 65 and 75 mmHg showed increased renal perfusion, with increased urine output, and less likely to require RRT. Furthermore, noradrenaline administration in patients with septic shock becomes an option for optimizing renal perfusion. The target of MAP in patients with septic shock differs depending on the history of blood pressure in patients, and patients with a normal history of takanan do not show significant gains for achieving MAP targets [35].

The use of loop diuretics such as furosemide to prevent fluid retention was said effective for inducing diuresis in children and adults. Low doses of diuretics (furosemide = 0.2 mg/kg/dose) may prevent the acute episode from hypovolemia. Continuous administration of furosemide infusions (0.1–0.3 mg/kgbb/day) may also be performed, and both can maintain drug concentrations in the renal tubules and prevent compensatory mechanisms of sodium reabsorption. A decrease in blood volume is also avoided to avoid hemodynamic deterioration. The use of long diuretics can cause resistance and known to use combination of loop diuretic and thiazide are also said to be effective [23].

The use of sedation drugs may cause vasiness and increase hemodynamic instability and thus increases the risk of excessive fluid administration. Provision of sedation also makes the patient should bed rest and is a risk factor for microvascular dysfunction and eventually fluid fertilization returns. This of course increases the time of ventilator use and increases the length of stay in the ICU and the hospital [36].

## 5. Conclusion

Fluid overload is an event that is often found in the intensive care room of children. This is in because the more severe the patient the more fluid administered, not only through infusion, but the provision of drugs and nutrients are also no less. Some recent research has found that fluid overload has many negative effects, particularly, in patients who have both sepsis and ARDS. In sepsis and ARDS patients, the initial fluid administration is able to increase disease survival rate but at 48, 72 and 96 h of fluid administration may result in an increase in mortality. Strength monitoring and restriction of fluid volume after resuscitation phase become an important step in order not to fall on fluid overload. Resuscitation should be subjective, and when the hemodynamic is stable, the volume of fluid should be handled either by direct reduction or by diuretics. Fluid overload generally associated with increased mortality, morbidity, duration of mechanical ventilation, length of hospitalization and the need for renal replacement therapy (RRT).

## Author details

Dyah Kanya Wati

Address all correspondence to: dyahpediatric@yahoo.com

Critical Care Medicine, Udayana University Sanglah Hospital, Denpasar, Bali, Indonesia

## References

[1] Willson DF, Thomas NJ, Tamburro R, Truemper E, Truwit J, Conaway M, et al. The relationship of fluid administration to outcome in the pediatric calfactant in acute respiratory distress syndrome trial. Pediatric Critical Care Medicine. 2013;**14**:666-672

[2] Flori HR, Church G, Liu KD, Gildengorin G, Matthay M. Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury. Critical Care Research and Practice. 2011;**2011**:854142

[3] Arikan AA, Zappittelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatric Critical Care Medicine. 2012;**13**(3):253-258

[4]   Sinitsky L, Walls D, Nadel S, Inwald DP. Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: Retrospective cohort study. Pediatric Critical Care Medicine. 2015;**16**:205-209

[5]   Semler MW, Rice TW. Sepsis resuscitation: Fluid choice and dose. Clinics in Chest Medicine. 2016;**37**(2):241-250. DOI: 10.1016/j.ccm.2016.01.007

[6]   Sutawan RIB, Wati DK, Suparyatha IB. Association of fluid overload with mortality in pediatric intensive care. Critical Care and Shock. 2016;**19**(1):8-13

[7]   Vincent JL et al. Sepsis in European intensive care units: Results of the SOAP study. Critical Care Medicine. 2006;**34**:344-353. PubMed: 16424713

[8]   Aditianingsih D, George YW. Guiding principles of fluid and volume therapy. Best Practice & Research. Clinical Anaesthesiology. 2014;**28**(3):249-260

[9]   Lopes CLS, Piva JP. Fluid overload in children undergoing mechanical ventilation. Revista Brasileira de Terapia Intensiva. 2017;**29**(3):346-353. DOI: 10.5935/0103-507X.20170045

[10]  Subramanian S, Ziedalski TM. Oliguria, volume overload, $Na^+$ balance, and diuretics. Critical Care Clinics. 2005;**21**(2):291-303

[11]  Ketharanathan N, McCulloch M, Wilson C, Rossouw B, Salie S, Ahrens J, et al. Fluid overload in a South African pediatric intensive care unit. Journal of Tropical Pediatrics. 2014;**60**(6):428-433

[12]  Wang N, Jiang L, Zhu B, Wen Y, Xi XM, Beijing acute kidney injury trial (BAKIT) workgroup. Fluid balance and mortality in critically ill patients with acute kidney injury: A multicenter prospective epidemiological study. Critical Care. 2015;**19**:371

[13]  Lorraine B. Pathophysiology of acute lung injury and the acute respiratory distress syndrome. Seminars in Respiratory and Critical Care Medicine. 2006;**27**(4)

[14]  Alphonsus CS, Rodseth RN. The endothelial glycocalyx: A review of the vascular barrier. Anaesthesia. 2014;**69**(7):777-784

[15]  Burke-Gaffney A, Evans TW. Lest we forget the endothelial glycocalyx in sepsis. Critical Care. 2012;**16**(2):121. DOI: 10.1186/cc11239

[16]  Murphy LS, Wickersham N, McNeil JB, et al. Endothelial glycocalyx degradation is more severe in patients with non-pulmonary sepsis compared to pulmonary sepsis and associates with risk of ARDS and other organ dysfunction. Annals of Intensive Care. 2017;**7**:102. DOI: 10.1186/s13613-017-0325-y

[17]  Zhang L, Zhu G, Han L, Fu P. Early goal-directed therapy in the management of severe sepsis or septic shock in adults: A meta-analysis of randomized controlled trials. (Research article) (Report). 2015;**13**:71

[18]  Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. Critical Care Medicine. 2011;**39**(2):259-265

[19] Raman S, Peters MJ. Fluid management in the critically ill child. Pediatric Nephrology. 2014;**29**(1):23-34

[20] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee Including the Pediatric Subgroup. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Critical Care Medicine. 2013;**41**(2):580-637

[21] Ogbu OC, Murphy DJ, Martin GS. How to avoid fluid overload. Current Opinion in Critical Care. 2015;**21**(4):315-321

[22] Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA, CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. The New England Journal of Medicine. 2012;**367**(20):1901-1911. Erratum in Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. [The New England Journal of Medicine 2016]

[23] Ingelse SA, Wösten-van Asperen RM, Lemson J, Daams JG, Bem RA, van Woensel JB. Pediatric acute respiratory distress syndrome: Fluid management in the PICU. Frontiers in Pediatrics. 2016;**4**

[24] Carsetti A, Cecconi M, Rhodes A. Fluid bolus therapy: Monitoring and predicting fluid responsiveness. Current Opinion in Critical Care. 2015;**21**(5):388-394

[25] Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Annals of Intensive Care. 2011;**1**(1):1

[26] Caille V, Jabot J, Belliard G, Charron C, Jardin F, Vieillard-Baron A. Hemodynamic effects of passive leg raising: An echocardiographic study in patients with shock. Intensive Care Medicine. 2008;**34**(7):1239-1245

[27] Walker LJ, Young PJ. Fluid administration, vasopressor use and patient outcomes in a group of high-risk cardiac surgical patients receiving postoperative goal-directed haemodynamic therapy: A pilot study. Anaesthesia and Intensive Care. 2015;**43**(5):617-627

[28] Joosten A, Alexander B, Cannesson M. Defining goals of resuscitation in the critically ill patient. Critical Care Clinics. 2015;**31**(1):113-132

[29] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. The New England Journal of Medicine. 2001;**345**(19):1368-1377

[30] Kelm DJ, Perrin JT, Cartin-Ceba R, Gajic O, Schenck L, Kennedy CC. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluidrelated medical interventions and hospital death. Shock. 2015;**43**(1):68-73

[31] Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM, ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. The New England Journal of Medicine. 2015;**372**(14):1301-1311

[32] Rewa O, Bagshaw SM. Principles of fluid management. Critical Care Clinics. 2015; **31**(4):785-801

[33] Grissom CK, Hirshberg EL, Dickerson JB, Brown SM, Lanspa MJ, Liu KD, Schoenfeld D, Tidswell M, Hite RD, Rock P, Miller RR 3rd, Morris AH, National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome. Critical Care Medicine. 2015;**43**(2):288-295

[34] Moussa MD, Scolletta S, Fagnoul D, Pasquier P, Brasseur A, Taccone FS, et al. Effects of fluid administration on renal perfusion in critically ill patients. Critical Care. 2015;**19**:250

[35] Piva J, Alquati T, Garcia PC, Fiori H, Einloft P, Bruno F. Norepinephrine infusion increases urine output in children under sedative and analgesic infusion. Revista da Associação Médica Brasileira (1992). 2014;**60**(3):208-215

[36] Lunardi N, Bryant M, Smith K, Lowson S. Early mobilization in critically ill patients. ICU Director. 2012;**3**(1):17-20

# Infections in ICU

# Infections and Multidrug-Resistant Pathogens in ICU Patients

Muntean Delia and Licker Monica

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79229

**Abstract**

This chapter aims to highlight the main types of infections in the ICU, in order to improve diagnostic and therapeutic management. Risk factors for patients hospitalised in the ICU will be raised: the increasing use of invasive devices and procedures, aggressive antimicrobial therapies, surgical interventions, immunosuppressive treatments or co-morbidities responsible for immune deficiencies. Starting from the rising mortality risk among patients with hospital-acquired infections (HAI), in the case of failure to control the pathogen in the first 24–48 h, we will tackle about the prevention, reduction and control of the emergence of resistant pathogens. The rational administration of antibiotics will also be addressed, with the aim of reducing adverse reactions, including secondary infections, decreasing the mortality rate, length of hospital stay and costs of health care.

**Keywords:** ventilator-associated pneumonia, intra-vascular catheter-related bacteraemia, sever sepsis, septic shock, antimicrobial treatment, multidrug resistance

## 1. Introduction

Modern medicine is a tributary to a continuously increasing degree of diagnostic and therapeutic invasiveness. In particular, intensive care units (ICUs) are confronted with increasing number of patients with marked co-morbidities, severe acute pathology or immune suppression, and intrinsic infectious risk factors. Additionally, given the pathogenicity changes of potentially hospital-acquired pathogens, most healthcare-associated infections (HCAIs) are caused by multidrug-resistant organisms (MDRO).

## 2. ICU infections

### 2.1. Severe respiratory infections

Pneumonia is one of the infections frequently requiring hospital admission and urgent anti-microbial treatment due to the risk of rapid evolution to respiratory and multiple organ failure, especially in immunocompromised patients, or when caused by MDRO. The diagnosis of severe pneumonia requires ICU admission given the need for assisted ventilation or oxygen therapy, in the presence of radiological changes, confirming the rapid progression, as well as the evolution towards sepsis [1, 2].

Community-acquired pneumonia (CAP) is caused by bacteria in 85% of cases, the most frequently involved pathogens being *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Severe CAP cases may also be produced by other pathogens (influenza viruses, coronaviruses, Hanta virus, *Legionella*).

Pneumonia may trigger acute myocardial infarction in patients with heart diseases, while in splenectomised patients or with spleen dysfunction, *S. pneumoniae* may cause severe sepsis with lethal outcome within 12–24 h from onset, even under antibiotic therapy.

The treatment of CAP must cover both typical and atypical pathogens. Clinical studies have shown that monotherapy with respiratory fluoroquinolones or tigecycline is almost as effective as therapy with antibiotic associations (ceftriaxone plus doxycycline, azithromycin, or respiratory quinolones) [3].

On the other hand, presently ICUs are especially confronted with respiratory infections acquired during hospitalisation. According to 2012/506/EU European Parliament Decision, hospital-acquired pneumonia (HAP) occurs 48 h or more after admission and was not incubating at the time of admission, while ventilated-associated pneumonia (VAP) arises in 48 h after endotracheal intubation [4]. The microorganisms involved in the aetiology of these pneumonia cases originate in the oropharyngeal or upper airways colonisation flora or by direct inoculation of contaminated solutions, via an endotracheal catheter, or exogenous contamination of respiratory equipment caused by health care staff.

The hospital-acquired risk factors associated with this type of infection are:

- long time sedation,
- general anaesthesia with endotracheal intubation,
- other invasive procedures: bronchoscopy, nasogastric catheterisation,
- prolonged use of assisted ventilation,
- reintubation, change of ventilation circuits at intervals under 48 h,
- post-trauma intubation,
- tracheostomy,
- corticotherapy or other immunosuppressive treatments,

- antibiotic therapy, administration of antacids or $H_2$ blockers, barbituric therapy after cranial traumas,

- thoracic or upper abdominal surgery,

- emergency surgery,

- administration of over 4 units of blood before the surgical intervention [5, 6].

These factors disturb respiratory functions leading to obstructions, decreased pulmonary volume, decreased filtration of inhaled air, and decreased secretion clearance. The insertion of an endotracheal tube allows the direct access of pathogens into the lower airways or may cause lesions of the epithelial mucosa, which represent breaches. Additionally, inadequate hand hygiene of medical personnel, lack of adherence to universal precautions, errors in decontamination of equipment or in the practice of endotracheal aspiration may favour not only cross-contamination but also the direct access of a massive bacterial inoculum.

This pneumonia is caused by a wide range of pathogens, and it may be plurietiological and is only rarely caused by viruses or fungi. The aetiological agents frequently involved in such infections are not only Gram-negative bacilli (*Pseudomonas aeruginosa, Klebsiella* spp., *Escherichia coli*) but also Gram-positive cocci such as *Staphylococcus aureus*. The frequency of MDRO is increasing and influences the treatment, as in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas*, fluoroquinolones, antipseudomonal penicillins and cephalosporins, extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL), *Acinetobacter baumannii*, etc. The risk factors for MDRO infections are the use of antibiotics during the previous 90 days, the onset of pneumonia after 4 days of hospitalisation, circulation of such pathogens in the health care unit in question, as well as the presence of comorbidities (immune suppression or immunosuppressive treatments).

The diagnosis of HAP should be rapidly reached, and the antibiotic treatment has to be promptly introduced, and any delay potentially aggravates the evolution and prognosis. The first antibiotic of choice depends on infection severity, patient's risk factors, and the number of hospitalisation days accumulated until the onset of pneumonia.

The empirical treatment of HAP or VAP occurring during the first five hospitalisation days in patients without risk factors for MDRO must include antibiotics active against not only aerobic Gram-negative bacilli (*Enterobacter* spp., *E. coli*, *Klebsiella* spp., *Proteus* spp., *Serratia* spp.), pathogens with respiratory tropism (*Haemophilus influenzae* and *Streptococcus pneumoniae*), but also methicillin-sensitive *S. aureus* (MSSA). Recommendations include therapeutic schemes based on ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) or ampicillin-sulbactam or ertapenem (**Figure 1**).

In the case of patients with HAP or VAP who are at risk for MDRO infection, regardless of the infection's severity, the antibiotic treatment must be directed against *P. aeruginosa, K. pneumoniae* (ESBL-producing strains), *Acinetobacter* spp. and MRSA. Antibiotic associations including antipseudomonal cephalosporins (ceftazidime), an antipseudomonal carbapenem (imipenem) or beta-lactam/beta-lactamase inhibitors (piperacillin-tazobactam), will be administered, in association with antipseudomonal fluoroquinolones (ciprofloxacin) or an
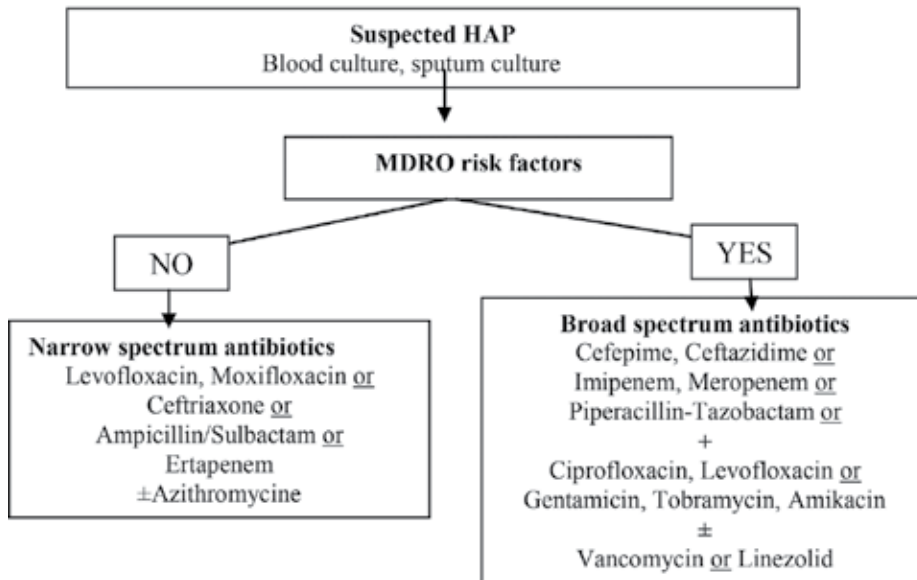
**Figure 1.** Antibiotic therapy in HAP.

| Antibiotic | Adult Doses |
|---|---|
| **Broad-spectrum cephalosporins** | |
| Cefepime | 1-2 g every 8-12 hours |
| Ceftazidime | 2 g every 8 hours |
| **Carbapenems** | |
| Imipenem | 500 mg every 6 hours or 1 g every 8 hours |
| Meropenem | 1 g every 8 hours |
| **Betalactam/ beta-lactamase inhibitor** | |
| Piperacillin-tazobactam | 4.5 g every 6 hours |
| **Aminoglycosides** | |
| Gentamicin | 7 mg/kg/day |
| Tobramycin | 7 mg/kg/day |
| Amikacin | 20 mg/kg/day |
| **Fluoroquinolones** | |
| Levofloxacin | 750 mg/day |
| Ciprofloxacin | 400 mg every 8 hours |
| **Anti-MRSA antibiotics** | |
| Vancomycin | 15 mg/kg every 12 hours |
| Linezolid | 600 mg every 12 hours |

**Table 1.** Empirical antibiotic treatment of HAP with MDRO.

aminoglycoside (tobramycin) and vancomycin or linezolid, to cover MRSA. If a *Legionella* infection is suspected, a macrolide (azithromycin) must also be associated [7] (**Table 1**).

The duration of the antibiotic treatment in HAP must be adjusted to the severity of the disease, the time required to obtain clinical improvement and the aetiological agent, but it has to exceed with at least 3 days the time to clinical improvement. The clinical response occurs after

at least 48–72 h, a period during which the recommendation is to maintain the therapeutic scheme. If, after this interval of empirical treatment, the clinical status of the patient did not improve, the therapeutic scheme must be broadened, potential complications (pleurisy, pulmonary abscess) and/or non-infectious causes must be sought.

## 2.2. Bacteraemia and septicaemia

### 2.2.1. Generalised septicaemic infections

The generalised septicaemic infection is an infection with an unpredictable outcome, high severity and increased mortality in the absence of adequate treatment. The correct choice of empirical antibiotic treatment depends on the intelligent use of clinical knowledge and epidemiological and microbiological data regarding the pathology in the area where the patient comes from. The lack of knowledge on the local resistance prevalence is a predictive factor for an incorrect treatment. The basic principle, which guides the treatment of the critical patient, is to rapidly initiate antibiotic treatment at correct doses, concordant with the pharmacokinetic and pharmacodynamic characters of the chosen drug and to adapt the treatment to the changes occurring in the clinical evolution and to the results of the antimicrobial sensitivity tests as soon as these become available.

Immediately after a patient with suspected sepsis is admitted, an attentive anamnesis and a thorough clinical examination are conducted in order to establish the entry and the location of the primary and secondary septic sites. The first emergency microbiological investigations are conducted (repeated blood cultures, cultures from secretions, lesions, urine, sputum, exudates, pleural fluid, etc.) together with evaluations of the renal, hepatic functions and state of consciousness, thus determining the severity of the case [8, 9].

The practical approach includes the emergency admission of the patient into the ICU where prevention or correction of hypovolemia, functional and metabolic dysfunctions are attempted, concomitantly with the prompt initiation of antibiotic treatment according to the maximal probability criterion.

The correct antibiotic treatment targets the resident microbial flora in the organ presumed to be the source of the infectious process.

The empirical treatment of sepsis consists of the association of bactericidal antibiotics with synergistic actions or monotherapy with an ultra-broad-spectrum antibiotic; antibiotics are administered intravenously in order to rapidly achieve an effective concentration in the infection site.

Empirical antibiotic therapy proved to be equally effective in beta-lactam-aminoglycoside associations, monotherapy with carbapenems, broad-spectrum penicillins/beta-lactamase inhibitors (ticarcillin/clavulanic acid, piperacillin/tazobactam) or third- and fourth-generation cephalosporins [10].

The aetiology of sepsis varies with the age of the patient, and the empirical treatment must be adapted to the most probable aetiology, but correlated with age, weight and associated pathology.

Adults with severe sepsis of unknown source must be treated with antibiotics effective against Gram-negative bacilli, *Staphylococcus aureus*, streptococci, respectively carbapenems (meropenem or imipenem) plus vancomycin. Septic shock requires the urgent refilling of the vascular system by infusions with saline solutions until the central venous pressure is re-established (over 80 mm at 6 h from hospital admission); at the same time, the primary source of infection is investigated, blood culture is collected and the first dose of antibiotic is administered, knowing that the time from admission to the initiation of antibiotic therapy is the strongest prognostic factor.

Patients admitted in a state of septic or toxic-septic shock will not be treated with beta-lactam (The bacterial load is very high, the pathogens are in a stationary phase with low protein synthesis, hence with a low synthesis of penicillin-binding proteins, so antibiotics lack their target.)

Colistin has a rapid antibacterial effect completed by a significant post-antibiotic effect against *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*. The most effective administration regimen is at 8 h. Colistin proved an important alternative in the treatment of MDR Gram-negative bacilli. Resistance to colistin is caused by sub-optimal doses. Colistin dosage must be optimised, as this antibiotic is the last option in the treatment of MDRO [11–13].

When a biliary infection is suspected to be at the origin of bacteraemia, the most frequently encountered bacteria are enterococci and aerobic Gram-negative bacilli, which respond well to piperacillin/tazobactam or ticarcillin/clavulanate; alternatively, ceftriaxone, ciprofloxacin or levofloxacin associated to metronidazole may be administered.

A great part (around 25%) of sepsis cases occur as a result of community or hospital-acquired urinary tract infections (UTI), evolving with a renal or complication of prostatic parenchyma. In such cases, the time from hospital admission to the initiation of antibiotic treatment is also decisive for the evolution. After collection of samples for blood and urine cultures, the first dose of broad-spectrum antibiotic active against *E.coli*, *Proteus* spp., *Enterobacter* spp., *Klebsiella* spp., *P. aeruginosa* is administered; more rare cases of sepsis of urinary origin may be caused by Gram-positive bacteria (15%) or by *Pseudomonas* spp., especially in patients with immune deficits. For an effective treatment of community-acquired urosepsis, depending on the type of local susceptibility, a third-generation cephalosporin or a fluoroquinolone may be indicated; in urosepsis following urologic surgery in patients with long-term urinary catheters, the association of a third-generation cephalosporin active against *Pseudomonas* or piperacillin/tazobactam with an aminoglycoside or a carbapenem is useful, this association being required to cover MDRO [14].

It should be noted that treatment in sepsis is complex, antibiotic therapy being accompanied with measures to eradicate the entry site and septic metastases, to correct tissue hypoxia and to maintain hydro-electrolyte and acid-base balance.

### 2.2.2. Infections associated with invasive devices

Invasive devices (endotracheal, intra-vascular catheters) increase the risk of HCAI especially with MDRO, by colonisation and biofilm formation on the internal surface of these devices. All types of intra-vascular devices may become complicated with blood infections, but arterial

catheters used for the haemodynamic monitoring and peripheral catheters show lower infection risks than central venous caterers (**Table 2**).

The removal of intra-vascular, gastric or bladder catheters, neurosurgical shunts, etc. as soon as they are no longer needed, represents an infection prevention measure. Both their insertion and removal is done by specialised staff, trained to work under sterile conditions, avoiding the risk of contamination. Knowing that invasive devices, catheters included, are the most frequent cause of HCAIs, their insertion must be conducted under aseptic conditions, choosing the most suitable site (for instance, sub-clavian rather than femoral), after ensuring the asepsis of the cutaneous area, preferably with chlorhexidine, and not with alcohol or iodine solutions. In severely immunocompromised patients, the recommendation is to use antibiotic-impregnated catheters. Clinical studies confirm the significant reduction in catheter-associated infections when these are removed as soon as their role is no longer essential [15–17].

An increasing number of patients require central venous catheters for long periods of time (for haemodialysis, total parenteral nutrition, chemotherapy), which favours complications such as thrombosis or infection. Central venous catheter-associated bacteraemia imposes the removal of the catheter and systemic administration of antibiotics. The clinical decision to remove a catheter suspected of infection relies on the presence of local infection signs. The decision to maintain the device is made in the absence of severity signs in patients with technical difficulties of catheter reinsertion in a new site.

There are situations when catheters may not be removed or replaced (lack of venous approach, counter indication of a new intervention, etc.). In such cases, attempts are made to save the venous line by eliminating the intra-luminal colonisation before the onset of bacteraemia or, once bacteraemia is present, the general administration of antibiotic is associated with exposing the inner surface of the catheter, after its closure, at a very high concentration of the adequate antibiotic meant to eradicate the colonisation. This technique proved effective in the case of Gram-negative bacilli and coagulase-negative staphylococci, but it is not recommended in colonisations with *S. aureus* [18].

### 2.3. Urinary tract infections

UTIs are the most frequent HCAIs. In most hospitals, catheter-related bacteriuria represents 40% of all HCAI within 1 year. The decision to treat is made after discriminating between the presence of bacteria (colonisation) and symptomatic infectious processes. The signs of

| Risk factors | Risk distribution |
|---|---|
| Type of catheter | Polyvinylchloride > teflon > polyurethane, metallic |
| Catheter site | Central > peripheral |
| | Femoral > jugular > subclavian |
| | Lower limbs > upper limbs |
| Type of placement | By incision > percutaneous |
| Duration of placement | over 72h > under 72h |
| Manner of placement | In emergency > selective |
| Experience of medical staff | Unexperienced staff > specially trained teams |

**Table 2.** Distribution of the infection risk in the intra-vascular catheterisation.

catheter-associated UTIs are fever, lateral lumbar pain, sensitivity in the costovertebral angle, haematuria and delirium with recent onset. After catheter removal, pollakiuria or dysuria may be present.

The Infectious Disease Society of America defines asymptomatic bacteriuria as the absence of symptoms with the presence of over $10^5$ colony forming units/ml of one or more bacterial species in a catheterised patient. In most cases of asymptomatic bacteriuria, the treatment led to the temporary sterilisation of urine and not to the eradication of pathogens [19]. Additionally, in 33–50% of patients, after catheter removal, the bacteriuria spontaneously resolved. This is why treating an asymptomatic bacteriuria increases the risk of antimicrobial resistance or of adverse reactions associated with useless antibiotic treatment.

Some pathogenic bacteria produce biofilms, which consist of an adherent layer of microorganisms and their extracellular products. The biofilm protects the pathogens against the host's defence mechanisms and against antibiotic therapy. Migration to the urinary bladder occurs in 1–3 days. The duration of catheterization is an important risk factor, with almost all patients who are catheterised for more than 30 days developing bacteriuria. These patients are at risk of upper urinary tract inflammation, which increases the risk of bacteraemia. Infections linked to long-term catheterisation are often polymicrobial, which involves a broad-spectrum treatment.

The selection of antibiotics used for the treatment of catheter-associated UTIs depends on the result of the microscopical examination, as well as on the colonial characters. In 60–80% of cases, the causative agent is a Gram-negative bacillus (*E.coli*, *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp.). The remaining 20–40% is caused by Gram-positive bacteria, most often species of staphylococci or enterococci. The empirical treatment has to take the following factors, which increase the risk of antibiotic resistance: the duration of hospitalisation, previous administration of antibiotics, and local resistance patterns.

Urinary fluoroquinolones (ciprofloxacin and levofloxacin) are administered to patients with mild and moderate infections, who are considered haemodynamically stable and do not present an altered mental status. Moxifloxacin is not recommended, as it does not reach effective urine concentrations. Broad-spectrum cephalosporins, ceftriaxone or cefepime, may also be used. In patients with urosepsis or in those haemodynamically unstable (hypothermia, tachycardia over 90/minute, tachypnoea over 20 respirations/minute or $P_{CO_2}$ under 33 mmHg, leukocytosis over 12,000/mm$^3$ or leukopenia under 4000/mm$^3$) piperacillin-tazobactam is administered.

In medium clinical forms, ciprofloxacin, 400 mg iv, for every 12 h or levofloxacin 500 mg iv /24 h or ceftriaxone for 1 g iv/day are administered.

The recommended treatments in severe forms include: cefepime 2 g iv/12 h, ceftazidime 2 g iv/8 h, imipenem 500 mg iv/6 h, doripenem 500 mg iv/8 h, meropenem 1 g/8 h and piperacillin/tazobactam 3.375 g iv/6 h.

The treatment of UTIs associated with bladder catheterisation is done with antibiotics for 3 days in women aged over 65 years, from whom the catheter has been removed; otherwise, the treatment is given for 7 days. The duration of levofloxacin treatment is 5 days.

Most hospital-acquired UTIS are expensive and may be prevented. The implementation of protocols based on present guidelines will reduce the inadequate use, as well as the antimicrobial resistance. When catheterisation is necessary, its duration should be limited. In case infections occur, the empirical treatment should be conducted according to the suspected pathogens and on the hospital's antibiogram. When the results of cultures become available, antibiotics narrow their spectrum. The treatment should be limited to 7–14 days, depending on the response to treatment. Catheter removal is a key factor because catheterisation increases the risk for hospital-acquired UTI and other complications, resulting in prolonged hospitalisation and increased costs [20, 21].

## 2.4. Intra-abdominal infections

Intra-abdominal infections include a series of diseases with variable severity, from uncomplicated appendicitis to faecal peritonitis. Uncomplicated infections involve a single organ and may not reach the peritoneum, and they may be solved either by surgical resection or by administration of antibiotics. Complicated intra-abdominal infections are those which extend to the peritoneum causing localised or generalised peritonitis; in order to solve these, the infection source must be solved by both surgery and antibiotic therapy.

The antimicrobial therapy of intra-abdominal infections, which are to be solved percutaneously or by surgery, has the following goals: to accelerate the elimination of the infecting microorganisms, to decrease the recurrence risk of the intra-abdominal infection, to shorten the clinical evolution, to limit the expansion of the infection to the abdominal wall and to decrease the risk of generalisation of the infectious process.

The antibiotic therapy is initiated after hydroelectrolyte rebalance, the restored volemia determining the restoration of the visceral perfusion and a better distribution of the medication. Moreover, this diminishes the side effects of antibiotics, which have been exacerbated by the deficitary perfusion of internal organs.

The empirical antibiotic treatment is initiated in concordance with the most probable microbiological spectrum, the type and density of germs being dependant on the level where the perforation of the digestive tract has occurred. By gastric, duodenal and proximal jejunal perforations, a low number of aerobic Gram-positive and anaerobic Gram-negative bacteria, generally sensitive to cephalosporins, are released into the peritoneum. *Candida albicans* has also been isolated, but antifungal treatment is only required in the case of patients under immunosuppressive treatment or in patients with recurrent intra-abdominal infections. The perforations of the distal small intestine often evolve as localised abscesses and peritonitis only takes place when these are ruptured. The intra-abdominal infections propagated from the colon into the peritoneum are caused by anaerobic or facultative anaerobic Gram-negative bacteria; *Bacteroides fragilis* is sometimes present.

The selection of the antibiotic should then be guided by the results of the cultures from the biological specimens obtained by percutaneous drainage or during the surgical intervention, but until these become available, it is necessary and useful to perform the microscopical examination directly on a Gram-stained smear. If high numbers of Gram-positive cocci are

present, these are very likely to be enterococci or other faecal streptococci, which imposes the association of vancomycin.

Aerobic and anaerobic Gram-negative cocci may be covered by administration of cefoxitin, ampicillin/sulbactam, piperacillin/tazobactam, imipenem, meropenem, moxifloxacin, while aerobic Gram-negative bacilli may be destroyed with aminoglycosides, second-, third- and fourth-generation cephalosporins, aztreonam, antipseudomonal penicillins or fluoroquinolones (ciprofloxacin, levofloxacin). It must be mentioned that ertapenem is not active on *Pseudomonas aeruginosa* and *Acinetobacter* spp., and in the case of critical patients infected with *P. aeruginosa*, the dose of meropenem must be increased to 1 g administered for every 6 h. Vancomycin-resistant enterococci produce extremely difficult to treat infections, the only useful antibiotic being daptomycin. Tigecycline has been approved for the treatment of complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, E. coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (*vancomycin-susceptible), MSSA, MRSA and some anaerobic bacteria [22].

The antibiotic, which is active only against Gram-negative bacilli and anaerobic bacteria, is metronidazole, for which no resistance has been reported.

The patients at high risk of unfavourable evolution and reserved prognosis have a high APACHE II score, poor nutritional status, significant cardiovascular diseases, immune suppression induced by medicines or by co-morbidities, while the infection source cannot be controlled. The predictive factors of therapeutic failure include the duration of the evolution prior to hospital admission, more than 2 days of presurgical treatment, as well as the presence of the MDRO. These patients should be treated similarly to those with hospital-acquired infections with carbapenems and vancomycin, but also considering the local antibiotic resistance.

The antibiotic treatment must be administered until the resolution of the clinical signs of infection (normalisation of the thermal curve, restoration of the intestinal transit) and normalisation of the biological inflammatory syndrome.

In cases with recurrent intra-abdominal infections, the diagnosis must be reassessed after 5–7 days of treatment and the investigations should be broadened (echography, CT). Often, the antibiotic therapy must be adjusted or a new surgical intervention is required in order to eliminate the site of infection.

### 2.5. Meningitis

The antibiotic treatment must be urgently initiated, immediately after blood collection for blood culture and after performing the lumbar puncture. Delayed administration of the first dose of antibiotic is associated with an aggravated prognosis, and it is a strong independent factor of increased mortality, exceeding the importance of disease severity upon hospital admission and of the isolation of a penicillin-resistant strain.

The most frequent cause of delayed antibiotic therapy is the missed diagnosis due to an atypical form of meningitis (absence of fever, headache or neck stiffness). Another possible cause of temporization is represented by scheduling the imagistic investigation immediately after admitting the patient in whom the spinal tap is not safe: risk of a cerebral hernia after

cerebrospinal fluid (CSF) collection, in cases of expansive intra-cranial processes accompanied by papilledema or focal signs. In this latter situation, computerised tomography (CT) or nuclear magnetic resonance (NMR) examinations should be conducted after blood collection for blood culture and after the first dose of antibiotic, despite the risk of excessive treatment.

*The antibiotic administration route* in meningitis is intravenous, which is capable to ensure the CSF bactericidal concentrations; the exception is for rifampicin, which may be administered orally and is useful in the treatment of meningitis caused by beta-lactam-resistant pneumococcus and coagulase-negative staphylococci.

*Antibiotic selection*: in the treatment of bacterial meningitis, bactericidal antibiotics able to cross the blood-brain barrier are administered, so that optimal CSF concentrations are ensured regardless of the meningeal inflammation degree (meningeal inflammation favours the penetration of the antibiotic in the sub-arachnoid space at the onset of the disease, but as the inflammation regresses under treatment, the concentration tends to decrease, so that higher doses are required as compared to other diseases) [23].

Patients with suspected bacterial meningitis will be initially treated with a broad-spectrum antibiotic concordant to the most probable aetiology, the selection being made depending on the age and comorbidities. After establishing the aetiology and antibiotic susceptibility of the isolated pathogen, the antibiotic therapy will be focused, maintaining the high doses and intravenous administration.

The lumbar puncture should be repeated after the first 24–36 h from the initiation of the treatment in order to assess CSF cytological, biochemical and bacteriological changes.

The immune competent adult with bacterial meningitis requires an initial antibiotic treatment aiming at meningococcus and pneumococcus, consisting in the association of ceftriaxone (2 g/12 h) or cefotaxime (2 g/6 h) with vancomycin (30–60 mg/kg/day for every 8 or 12 h); third-generation cephalosporins must be administered even if the antibiogram shows that the respective strain presents intermediate sensitivity or resistance, because vancomycin acts synergically and increases the efficiency of the therapy [24].

Patients with bacterial meningitis and compromised cell immunity due to pre-existing conditions or immunosuppressive treatment, but with conserved renal function, should be treated with vancomycin (60 mg/kg/day divided into two or three doses) plus cefepime (6 g/day divided into three doses) or meropenem (6 g/day divided into three doses).

If a *Listeria* infection is suspected, the empirical treatment may consist in the association between vancomycin and moxifloxacin (400 mg in a single daily dose) plus trimethoprim-sulfamethoxazole (10–20 mg/kg/day divided at 6 or 12 h).

The duration of the antibiotic treatment in meningitis is not standardised, but it should be individualised based upon the clinical response of each patient, but usually 7 days of treatment is sufficient for meningococcal and *H. influenzae* meningitis, 10–14 days for pneumococcal meningitis, 14–21 days for meningitis with *S. agalactiae* and 21 days or more for meningitis with *L. monocytogenes*; meningitis with aerobic Gram-negative bacilli requires antibiotic administration for 21 or 14 days after the last CSF sterile culture.

**Hospital-acquired bacterial meningitis (HABM)** may be the result of an invasive procedure (craniotomy, insertion of internal or external ventricular catheter, lumbar puncture, intrathecal medication, spinal anaesthesia), of a complicated cranial trauma or, in more rare cases, of an infectious metastasis in patients with hospital-acquired bacteraemia. Such meningitis is caused by microorganisms with different spectra from community-acquired cases, and the disease is the result of particular pathogenetic mechanisms.

Bacterial meningitis is a redoubtable complication of craniotomy, occurring in 0.8–1.5% of the patients who undergo this procedure. One-third of the post-craniotomy meningitis cases develop during the first week after the surgical intervention, another third during the second week and one-third after the second week from the intervention, sometimes even years after the surgical procedure. The risk of post-surgical meningitis may be minimised by the attentive use of surgical techniques, especially those which decrease the possibility of liquid fistulae. Other factors associated with meningitis after craniotomy include concomitant infection at the incision site and duration of procedure exceeding 4 h.

The incidence of meningitis associated with internal ventricular catheters (cerebrospinal shunt) used in the treatment of hydrocephaly varies between 4 and 17%. The most important causative factor is the colonisation of the catheter at the time of insertion so that most infections become manifest in less than 1 month from the procedure.

External ventricular catheters are used to monitor intra-cranial pressure or to temporarily deviate the CSF if there is an obstruction in the system or as a treatment component in cases of infection of the internal catheter. The rate of external catheter-associated infection is around 8%.

The incidence of meningitis after moderate or severe cranial trauma is 1.4%. The open cranial trauma is encountered in 5% of cranial trauma and is complicated by meningitis in 2–11% of cases. Most patients in whom meningitis occurs as a complication of closed cranial trauma present a skull base fracture, which creates a communication between the sub-arachnoid space and the sinus cavities, posing an infection risk of up to 25%. The average time interval between the trauma and the onset of meningitis is 11 days. The CSF leak is the major risk factor, even though most post-traumatic leaks are not diagnosed. Most fistulae resolve spontaneously within 7 days, a surgical intervention is recommended if the breach persists. The cranial trauma is the most frequent cause of recurrent meningitis.

The diagnostic procedure relies on neuroimagistic investigations, CSF analysis (cell count, biochemical tests for glucose, proteins, Gram staining, cultures) and blood cultures. Neuroimagistics is indicated in most patients as it allows the ventricular size evaluation and brings information on a possible poor functioning of the shunt or the presence of residual catheters after previous surgical interventions.

The most frequently encountered bacteria in these cases are Gram-negative bacilli (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), *S. aureus* and coagulase-negative staphylococci.

The empirical antibiotic therapy in HABM depends on the pathogenesis of the infectious process. In patients with meningitis occurring after neurosurgical interventions, or in patients with long-term hospitalisation after open cranial trauma or skull base fractures, vancomycin is associated with cefepime, ceftazidime or meropenem; the second antibiotic is selected

depending on the local chemotherapeutics susceptibility profiles of Gram-negative bacilli. The empirical treatment in skull base fracture or early after ENT surgery includes vancomycin plus a third-generation cephalosporin (cefotaxime, ceftriaxone). After isolating the involved pathogen, antimicrobial therapy is changed for an optimal management. Linezolid and daptomycin are effective in staphylococcal meningitis; linezolid has good pharmacokinetic properties—CSF penetration is around 80%.

The initiation of empirical treatment is recommended in all patients with post-surgical signs of meningitis; this is withdrawn after 72 h in case the results of CSF cultures are negative. The treatment must be individualised, especially in patients previously treated with antibiotics, in whom the treatment is continued despite the negative results of cultures.

Given the emergence of MDR Gram-negative bacilli, the antimicrobial therapy of HABM caused by these pathogens becomes problematic. This is especially true in cases of HABM caused by *Acinetobacter baumannii* species, bacteria with acquired resistance to third- and fourth-generation cephalosporins and even to carbapenems. The treatment of *Acinetobacter* meningitis includes meropenem associated with an aminoglycoside administered intra-ventricularly or intrathecally. If the identified isolate is resistant to carbapenems, intra-ventricular or intrathecal administration of colistin or polymyxin B will be given instead of meropenem.

Treatment protocols recommended depending on the pathogenesis of the infectious process:

- *Infection after neurosurgical procedure*—Gram-negative bacilli (including *P. aeruginosa*), *Staphylococcus aureus* and coagulase-negative staphylococci (*S. epidermidis*) may be involved. Vancomycin plus cefepime or meropenem are recommended.

- *Ventricular or lumbar catheter*—coagulase-negative staphylococci, *S. aureus*, Gram-negative bacilli (*P. aeruginosa*) and *Propionibacterium acnes* may be present. Vancomycin plus cefepime or meropenem are recommended.

- *Penetrating trauma: S. aureus*, coagulase-negative staphylococci, Gram-negative bacilli. Vancomycin plus cefepime or meropenem is administered.

- *Skull base fracture: Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*. Vancomycin plus a third-generation cephalosporin (ceftriaxone or cefotaxime) is recommended.

## 2.6. Infections of the skin and soft tissues

With the increasing incidence of MRSA, skin and soft tissue infections require more frequent admission of patients presenting tissue necrosis, fever, hypotension, intense pain, altered consciousness, respiratory, hepatic or renal failure, to the ICU. When choosing the therapeutic scheme, the possibility of a polymicrobial infection must be considered, with consecutive need to cover not only MRSA but also Gram-negative and anaerobic bacteria. An inadequate initial empirical treatment is associated with prolonged evolution and hospital stay [25].

Perianal infections and abscesses, infected decubitus ulcers, and moderate and severe infections of the diabetic foot frequently involve multiple aetiologies and require coverage for

streptococci, MRSA, aerobic and anaerobic Gram-negative bacilli until the results of micro-biological investigations become available.

In the case of patients with non-suppurative cellulitis, a beta-lactam antibiotic, such as cefazo-lin, may be initially prescribed, which is to be replaced in case of unsatisfactory clinical evolu-tion. The replacement will be made according to the result of the antimicrobial susceptibility test or with an antibiotic active on MRSA, if the pathogen has not been isolated in the culture. The empirical treatment of MRSA infections may include vancomycin, linezolid, daptomycin, tigecycline and telavancin. Linezolid, daptomycin, vancomycin and telavancin additionally also cover streptococcal infections and not only MRSA.

In case of a documented or suspected staphylococcal infection, the recommendation is to immediately initiate the antibiotic treatment according to maximal probability criteria and according to local data on the sensitivity of strains circulating in the respective area. The doses of antibiotic must be adequate, because sub-inhibitory concentrations favour the release of staphylococcal toxins and virulence factors (PVL—Panton-Valentine leukocidin), which trig-ger the onset of skin, lung or bone necrotic lesions. Catheters and intra-vascular devices must be removed. In cases with detected abscesses, these should be drained; the localised infection of a prosthetic joint requires the removal of the prosthesis, but if the infection is located on a valvular prosthesis, its removal is not always required.

The treatment of MRSA infections frequently includes the administration of vancomycin. The increased vancomycin consumption has posed an increasing selection pressure of staphylo-coccal strains resistant to this antibiotic. The concentration of vancomycin required to inhibit most *S. aureus* strains is 0.5–2 mg/l. The strains with a minimum inhibitory concentration (MIC) of vancomycin between 8 and 16 mg/l are classified as intermediate sensitive or VISA (vancomycin-intermediate *S. aureus*), while strains with MIC $\geq 32$ mg/l are considered resis-tant or vancomycin-resistant *S. aureus* (VRSA). The resistance mechanisms are different in the two types of strains: in VISA strains, the bacterial cell wall is thickened by the altered biosynthesis process and the glycopeptides targets are hidden in its thickness and in the case of VRSA strains, the target of glycopeptides is itself modified.

**Surgical wound infections** are another category of infections frequently confronting ICUs. In their most frequently polymicrobial aetiology, Gram-positive cocci (especially MRSA), *Enterobacteriaceae* and non-fermentative Gram-negative bacilli (*P. aeruginosa*) are among the most frequently isolated pathogens. The empirical treatment of these infections consists of associating cefepime or meropenem with an aminoglycoside or a fluoroquinolone.

Many extrinsic risk factors are inter-connected with intrinsic factors or are found in asso-ciation, for which reason, the Study on the Efficacy of Nosocomial Infections Control (SENIC), a risk index, has been proposed for surgical wound infections. When compared to the traditional Altemeier system, this index predicts the risk of post-surgical infection two times better and the inclusion of other items does not seem to improve its predic-tive capacity [26]. The National Surveillance System of Nosocomial Infections in the USA proposed the NNIS risk index, further completed with the item on the use of laparoscopic techniques (**Tables 3** and **4**).

| SENIC index | | | NNIS index | |
|---|---|---|---|---|
| Item | | Score | Item | |
| 1. Operating time > 2 ore | | 1 point | 1. Class ASA 3/ 4/ 5 | 1 point |
| 2. Abdominal surgery | | 1 point | 2. Contaminated or septic surgery | 1 point |
| 3. Contaminated or septic surgery | | 1 point | 3. Duration of surgical procedure > T (variable time depending on the operating procedure) | 1 point |
| 4. Presence of at least 3 diagnosis | | 1 point | 4. Use of laparoscopic technique | -1 point |
| SENIC score = Σ item 1,2,3,4 | | | NNIS score = Σ item 1,2,3,4 | |

**Table 3.** Risk indexes for post-surgical wound infections.

| Class | Classification | Infection rate | |
|---|---|---|---|
| | | With presurgical antibiotic prophylaxis | Without presurgical antibiotic prophylaxis |
| Class I | Clean surgery | 5.1% | 0.8% |
| Class II | Clean-contaminated surgery | 10.1% | 1.3% |
| Class III | Contaminated surgery | 21.9% | 10.2% |
| Class IV | Septic surgery | | |

**Table 4.** Risk of post-surgical wound infection depending on the Altemeier classification.

## 3. Management of antibacterial chemotherapeutic drugs

The choice of antibiotics is conditioned by:

- the characteristics of the isolated or suspected aetiological agent,

- patient characteristics, which may influence the efficiency and toxicity of the treatment (age, physiological status, comorbidities, infection site),

- pharmacodynamic and pharmacokinetic characteristics of the antibiotic (adsorption, tissue distribution, concentration in the infectious focus, metabolisation and elimination of the antibiotic).

In the case of the critical patients, the early administration of an effective antibiotic treatment is essential and determining, the time until the initiation of therapy being a strong predictor of mortality. A retrospective cohort study showed that the delay of effective treatment after the onset of recurrent or persistent hypotension was associated with an increased death risk; the survival rate in patients with treatment administered during the first hour was of 79.9%, with each hour of delay in antibiotic therapy leading to a 7.6% decrease in this rate [27].

*Optimization of doses*. The antibiotic requirement is calculated depending on the characteristics of the patient (age, weight, renal function), on the pathogenic microorganism, infection site

(endocarditis, pneumonia, meningitis, osteomyelitis) and the pharmacokinetic and pharmacodynamic characteristics of the drug [28].

The loading dose is probably the most important and depends on the distribution volume of the drug and on the intended plasmatic concentration, regardless of the renal function. Antibiotics are classified according to multiple criteria, one being the criterion, which influences the dosage: the doses of hydrophilic antibiotics (beta-lactam) must be increased during the first stages of sepsis, together with the increase in the extravascular space. The doses of lipophilic antibiotics are influenced by other factors, such as obesity [7, 28].

Before establishing the rational antibiotics administration regimen, the antimicrobial activity in time must be understood, i.e., the pharmacodynamics of the drug in question (the relationship between its serum concentration and its therapeutic effect). From a pharmacodynamic perspective, antimicrobial agents may be divided into:

- The bactericidal effect of beta-lactam antibiotics is independent of their concentration, as long as this exceeds the MIC and they do not possess a significant post-antibiotic effect (PAE) (The inhibition of bacterial growth continued for a variable period after the concentration of antibiotic at the infection site has dropped under the MIC.) The strategy to obtain optimal results is to increase the exposure time of microbes to plasmatic concentrations of antibiotic exceeding the MIC, which is accomplished by frequent doses, by the administration at short time intervals or by continuous infusion.

- The bactericidal effect of vancomycin, carbapenems, macrolides, clindamycin, azoles, linezolid is independent of their concentration, if this is higher than the MIC, but it is time dependent. The PAE is intermediate (The serum antibiotic levels may drop under the MIC for a short while.) The antibiotics in this group produce optimal results when administered in lower but with more frequent doses.

- The bactericidal effect of aminoglycosides, fluoroquinolones and metronidazole is dose dependent and has a significant post-antibiotic effect (Bacterial growth is prevented even if tissue levels decrease under the MIC for longer periods of time.) This is why higher doses, but at larger intervals, may be administered, with 2–4 h between the doses after being admitted, during which time the plasmatic concentration of these antibiotics may be undetectable, which reduces their nephrotoxicity.

The time-dependent bactericidal effect is achieved by optimising the duration of bacterial exposure to antibiotics, while the dose-dependent bactericidal effect is maximal when the antibiotic concentration is maximal [7].

Polymyxins are concentration-dependent antibiotics; they are active on carbapenemase-producing bacteria, and they are increasingly kept as last therapeutic option in infections with resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. We must underline the fact that if sub-optimal doses of colistin are administered, the pathogen gains resistance.

First-line antibiotic treatment in severe acute infections.

Severe acute infections are classified as community-acquired, healthcare-associated and hospital-acquired infections. For the practical assessment of a case, Yehuda Carmeli proposed a score, which allows the stratification of risk factors for the infections with resistant or MDRO, depending on the previous contact of the patient with the health care sector, on the existence in his/her medical history of antibiotic treatments, as well as on associated factors (immune suppression, co-morbidities):

Risk assessment for infections with resistant or MDR pathogens:

 a.  Contact with the health care sector:

   1.   No contact—1

   2.   Contact without invasive procedures—2

   3.   Repeated contacts with invasive procedures—3

 b.  Previous antibiotic treatment:

   1.   No antibiotics—1

   2.   With antibiotics—2

 c.  Characteristics of the patient:

   1.   Young, without co-morbidities—1

   2.   Elderly, with co-morbidities—2

   3.   Immunocompromised patient (AIDS, neoplastic diseases)—3

According to this score, the value 1 corresponds to community-acquired infections, the value 2 corresponds to HCAI and the value 3 to hospital-acquired infections. The Carmeli score may only be 1, 2 or 3, and it is given by the highest value obtained from the answers to the three categories of questions [29]. This classification allows a correlation between the type of infection, the most probable aetiology and the estimation of the antibiotic susceptibility of the microorganism in question.

The empirical or first-line treatment is especially important for the evolution of the infection; the delayed initiation of an effective antimicrobial treatment leads to increased morbidity and mortality, aggravated and generalised infections, as well as increased health care costs. If the initial treatment has not been effective, adding a new antibiotic or replacing the initial one with a broader spectrum antibiotic (escalation) will not increase the chance of favourable evolution. The adjustment of antibiotic treatment after the microbiological results become available might be tardy and ineffective, if the initial treatment has been inadequate, especially in the case of hospital-acquired infections (multivariate analysis have demonstrated that inadequate empirical treatment increased the risk of mortality). The association of antibiotics of different classes is useful in the initial treatment of infections with MDRO.
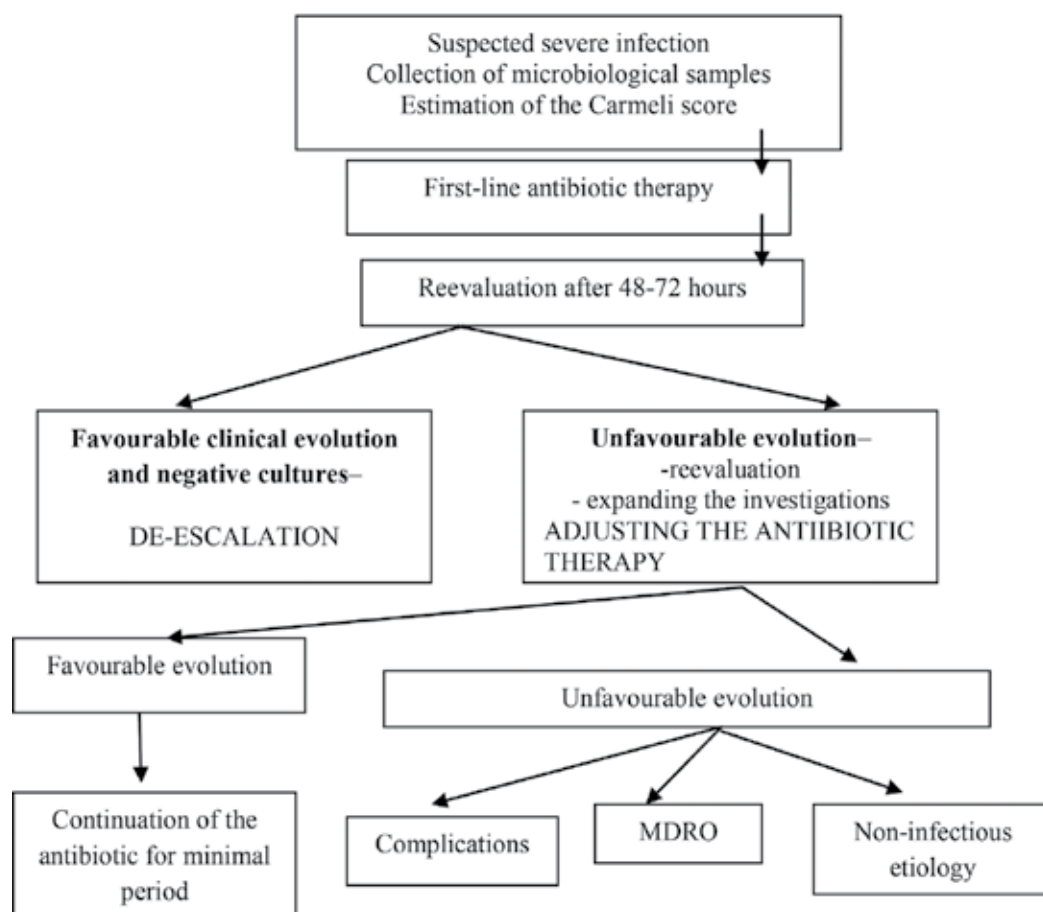
**Figure 2.** Algorithm for initiation of antibiotic therapy.

In patients with severe infections, the recommendation is to administer the antibiotic treatment during the first hour after the diagnosis, but not before collection of blood and other biological samples required for the identification of the aetiological agent and testing for its sensitivity to chemotherapeutics. Patients with meningitis will receive antibiotic treatment during the first 30 min after hospital admission, immediately after collection of blood and CSF [1, 10].

The empirical or first-line antibiotic treatment is initiated according to the most probable microbiological spectrum and consists of the administration of a broad-spectrum antibiotic (covering Gram-positive cocci, including MRSA and enterococci, as well as Gram-negative bacilli, including *Acinetobacter* spp., *Pseudomonas aeruginosa* and *Enterobacter* spp.) for a short period of time, i.e., for 2–3 days. Depending on the clinical evolution of the patient and on the results of microbiological tests, the initial treatment scheme may be modified by decreasing the number of antibiotics or reducing the spectrum (*de-escalation*). Narrowing the therapeutic regimen does not only refer to the shift from a broad-spectrum to a narrow-spectrum antibiotic, but also to adjusting (reducing) the doses and treatment duration [30].

The Principles of de-escalation are as follows:

- administration of an ultra-broad-spectrum antibiotic for a short period of time,

- identification of the aetiology within this covered period,

- replacement of the initial antibiotic with a narrow-spectrum antibiotic.

If, after 48–72 h of treatment with a broad-spectrum antibiotic, the status of the patient does not improve, the available microbiological data are attentively reanalysed and the possibility of MDRO infection, a non-bacterial or even a non-infectious aetiology, are considered. The evaluation must also include the possibility of a complication, such as the formation of an abscess, empyema, etc. [31].

Decreasing the risk of adverse reactions, the decreased selection pressure of resistant strains, as well as the reduction of costs represent the benefits of de-escalation and treatment cessation after a shorter time. Examples of benefits in the administration of antibiotics in short cures and/or reduction of the antibiotics spectrum include the decrease in the incidence of cases of diarrhoea with *Clostridium difficile* and of infections with resistant bacteria and *Candida* spp. (**Figure 2**).

## Author details

Muntean Delia and Licker Monica*

*Address all correspondence to: deliacristimuntean@yahoo.com

"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

## References

[1] Niederman MS, Craven DE, Bonten MJ, et al. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. American Journal of Respiratory and Critical Care Medicine. 2005;**171**:388-416

[2] Marin H, Kollef MLE, Baughman RP. Health care-associated pneumonia (HCAP): A critical appraisal to improve identification, management, and outcomes-proceedings of the HCAP summit. Clinical Infectious Diseases. 2008;**46**(Supl 4):S296-S334

[3] Rello J, Kollef M, Diaz E, Rodriguez A. Infectious Diseases in Critical Care. Berlin Heidelberg: Springer-Verlag; 2007. pp. 203-205

[4] https://publications.europa.eu/ro/publication-detail/-/publication/10ed460f-0711-11e2-8e28-01aa75ed71a1/language-ro

[5] ***CDC Bacterial Pneumonia, MMWR. 1997;**46**:RR1-RR85

[6]  Strausbaugh LJ. Nosocomial respiratory infections. In: Mandell GL, Bennett JE, Mandell Douglas DR, Bennett's, editors. Principles and Practice of Infectious Diseases. 6th ed. Vol. 2005. Elsevier Churchill Livingstone. pp. 3362-3369

[7]  Rello J. Importance of appropriate initial antibiotic therapy and deescaladation in the treatment of nosocomial pneumonia. European Respiratory Review. 2007;**16**(103):33-39

[8]  Burke AC: Bacterial sepsis. 2011. Available from: http://misc.medscape.com/pi/android/medscapeapp/html/A234587-business.html

[9]  Mackenzie I, Lever A. Management of sepsis. BMJ. 2007;**335**(7626):929-932

[10] Micek ST, Welch EC, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: A retrospective analysis. Antimicrobial Agents and Chemotherapy. 2010;**54**(5):1742-1748

[11] Lim LM, Neang Ly BS, Anderson D, et al. Resurgence of Colistin: A review of resistance, toxicity, pharmacodynamics and dosing. Pharmacotherapy. 2010;**30**(12):1279-1291

[12] Arnold RS, Thom KA, Sharma S, et al. Emergence of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Southern Medical Journal. 2011;**104**(1):40-45

[13] Lee J, Patel G, Huprikar S, et al. Decreased susceptibility to polymyxin B during treatment of carbapenem-resistant *Klebsiella pneumonia* infection. Journal of Clinical Microbiology. 2009;**47**:1611-1612

[14] Wagenlehne FM, Pilatz A, Naber KG, Weidner W. Therapeutic challenges of urosepsis. European Journal of Clinical Investigation. 2008;**38**(S2):45-49

[15] Barsiç B, Beus E, Marton E, et al. Nosocomial infections in critically ill infectious diseases patients: Results of a 7-year focal surveillance. Infection. 1999;**27**(1):20-26

[16] Beekmann SE, Henderson DK. Infections caused by percutaneous intravascular devices. In: Mandell GL, Bennett JE, Mandell Douglas DR, Bennett's, editors. Principles and Practice of Infectious Diseases. 6th ed. Elsevier Churchill Livingstone; 2005. pp. 3347-3360

[17] ***CDC Guideline for Prevention of Cateter-Related Nosocomial Infections. Vol. 51. MMWR; 2002. p. RR10

[18] Fernandez-Hidalgo N. Antibiotic-lock therapy for long-term intravascular catheter-related bacteraemia: Results of an open, non-comparative study. The Journal of Antimicrobial Chemotherapy. 2006;**57**(6):1172-1180

[19] Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical Infectious Diseases. 2011;**52**(5):e103-e120

[20] http://uroweb.org/wp-content/uploads/Guidelines_WebVersion_Complete-1.pdf

[21] Hopkins J. Antibiotic Guidelines 2015-2016. Treatment Recommendations for Adult Inpatients. Available from: insidehopkinsmedicine.org/amp

[22] Sartelli M. A focus on intra-abdominal infections. World Journal of Emergency Surgery. 2010;**5**:9

[23] Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clinical Microbiology Reviews. 2010;**23**(3):467-492

[24] Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clinical Microbiology Reviews. 2010;**23**(4):858-883

[25] Rajan S. Skin and soft-tissue infections: Classifying and treating a spectrum. Cleveland Clin J Med. 2012;**79**(1):57-66

[26] Talbot TR, Kaiser AB. Postoperative infections and antimicrobial prophylaxis. In: Mandell GL, Bennett JE, Mandell Douglas DR, Bennett's, editors. Principles and Practice of Infectious Diseases. 6th ed. Elsevier Churchill Livingstone; 2005. pp. 3533-3344

[27] Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical Care Medicine. 2006;**34**:1589-1596

[28] Morrell MR, Micek ST, Kollef MH. The management of severe sepsis and septic shock. Infectious Disease Clinics of North America. 2009;**23**(3):485-501

[29] Carmeli Y. The Role of Carbapenems: The Predictive Factors for Multi-Drug–Resistant Gram-Negatives. 2006. Available from: www.invanz.co.il/

[30] Kollef MH, Ward S, Sherman G, et al. Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. Critical Care Medicine. 2000;**28**:3456-3364

[31] Deresinski S. Principles of antibiotic therapy in severe infections: Optimizing the therapeutic approach by use of laboratory and clinical data. Clinical Infectious Diseases. 2007;**45**(supl 3):S177-S183

# Current Status of Colonization and Infection by Multiresistant Bacteria in the Spanish Intensive Care Unit: Resistance Zero Program

Miguel Ángel García García,
Alfonso Martínez Cornejo, David Arizo León and
María Ángeles Rosero Arenas

Additional information is available at the end of the chapter

## Abstract

Current medicine, highly technified, and capable of amazing achievements, is not possible without the support of antibiotics. The problem of antibiotic resistance is almost as old as the antibiotics themselves. But at present, it is a serious threat to public health. We have to fight against antibiotic resistance in the hospital and in the out-of-hospital environment. The Resistance Zero program, promoted by the Spanish Society of Intensive Medicine, has achieved through a multidisciplinary approach with collaboration between doctors, nurses, cleaning staff and microbiologists, to control the colonization and infection by multiresistant germs in the environment of the Intensive Care Unit.

**Keywords:** antibiotic resistance, multiresistant bacteria, intensive care unit, colonization, infection

## 1. General concepts

### 1.1. Global data

The emergence of antibiotic and their use in clinical practice is one of the greatest achievements of Medicine. In the mid-twentieth century, its use became widespread, and it was thought that a rapid and definite eradication of infectious diseases was possible. However, the first resistant bacteria soon appeared, and antibiotic resistance has developed into a serious public health problem. It is estimated that up to 60% of nosocomial infections are caused by resistant germs both in Europe and in the United States. The Center for Disease Control and prevention (CDC)

in the United States has estimated that the problem of antibiotic resistance is responsible for 2 million infections and 23,000 deaths per year with a direct cost of 20 billion dollars, and losses of productivity equivalent to 33 billion dollars [1]; the European Center for Disease Control, ECDC, have estimated that accounts for 25,000 deaths and 1.5 billion € per year by infections by multiresistant bacteria (MRB) [2]. Some consequences of this problem are: increased cost of health care, increased rates of failure of antibiotic treatment and increased mortality. This is not a problem limited to certain regions or countries and resistance can spread quickly in our globalized world.

### 1.2. Intensive care unit generalities

Intensive care unit (ICU) accounts for less than 10% of total beds in most hospitals, but more than 20% of nosocomial infections are acquired in ICU [3]. Acquired in ICU infections pose significant morbidity, mortality and expense; they are the most frequent cause of death in non-cardiac ICUs and 40% of all ICU expenses [4]. In comparison with patients from other areas of the hospital, ICU patients have higher chronic comorbidity, more severe acute physiological deterioration and are relatively immunosuppressed [5]. Its management also implies a high degree of invasiveness, with use of intravascular catheter, contact with a large number of health personnel—predisposing to colonization and infection—and are subjected to an increased colonization pressure [5].

When a patient goes to the hospital today, he undergoes a more effective and complete care than in previous years. Advances in diagnostic and therapeutic methods mean improvements in care and may be accompanied by a greater number of associated complications. All these data are magnified in ICU; ICU patients are more vulnerable to develop infections during their stay and to become colonized/infected with MRB. Overcrowding in closed areas of these severely ill patients with multiple comorbidities and subjected to invasive devices are risk factors for the development of nosocomial infections.

There is a clear relationship between the appearance of resistance and the highest antibiotic consumption. Infections due to resistant germs/MRB have limited therapeutic options, so inadequate empirical treatments are prescribed, the start of the correct treatment is delayed and therapeutic failures increase. All this leads to longer ICU stay, costs and mortality, with worse prognosis of the patient.

The highest density of MRB is observed in ICU. The importance of adequate and early treatment is greater in critically ill patients; for all above, it is necessary to implement programs for the prevention and treatment of multiresistant bacteria MRB, both in the ICU and in the community—a great number of MRB can be related to inadequate or excessively prolonged treatments in the general ward or outside the hospital.

### 1.3. Antibiotic resistance mechanisms

The mechanisms related to the emergence of resistance are varied. Resistance can be intrinsic or acquired. the first occurs in certain germs that are not innately sensitive to certain antibiotics, by a special membrane structure or related to the mechanism of the antibiotic. There may be at the molecular level: modifications in the targets (nucleic acid, ribosomes, action points

of certain antibiotics—such as penicillin-binding proteins, PBPs); alterations in the transmembrane passage (porins, mechanisms of uptake or active transport); enzyme production (beta-lactamases). The appearance of mutations in the genetic material of the bacteria or the transfer of resistance genes from other germs explains the transformation from sensible to resistant bacteria. The exposure to antibiotics induces the disappearance of a population sensitive, and the selection of resistant strains to the antibiotics that end up being predominant.

### 1.4. Definition of MRB

MRB are defined as those microorganisms resistant to three or more antibiotics, which must also have clinical relevance. The exception to this rule is methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) cases, in which the resistance condition is given by only one antibiotic. The phenomenon of resistance constitutes a medical problem, since it becomes a difficulty for the treatment and also epidemiological relevance, given the possibility of transmission of the outbreak. The ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and Enterobacter especies) are a specific group of bacteria with clinical relevance, associated with health care, and with the capacity to develop antibiotic resistance [6].

### 1.5. Description of the MRB

*P. aeruginosa* (Pa) has a predilection for humid environments and usually contaminates aqueous solutions such as disinfectants or soaps, mechanical ventilation equipment, fiberoptic bronchoscopes, and so on. Resistance may appear in the course of an antibiotic treatment. Its main mechanism of resistance is the presence of extended-spectrum beta-lactamases (ESBL) and alterations in permeability (porin mutations and expulsion pumps).

*Acinetobacter baumannii* (Ab) contaminates and endemically colonizes the hospital environment. It is capable of surviving and rapidly developing resistance to the main classes of antibiotics, more frequently in summer [7]. Some strains can survive to environmental drying form months, which facilitates transmission via contamination of fómites in the hospital. The health personnel is usually carrier of Gram-negative bacilli (GNB) (30%). Outbreaks have been described in relation to contaminated mechanical ventilation equipment and manual transmission. Infections have also been described in war wounds and in situations of natural disasters. Sixty-three percent of bacterial isolation from war wounds in Iraq and Afghanistan corresponded to this germ [8]. Infections tend to appear in patients with long stay in the ICU and health centers, dependent on mechanical ventilation, central catheter carriers, and with prior treatment with third-generation cephalosporins, fluorquinolones or carbapenemes. Although patients with Ab infection have high mortality, it is not clear whether mortality can be attributed to infection or to life-threatening conditions [9]. Several factors are associated with mortality: isolation in blood cultures, presence of signs of sepsis/septic shock, resistance to imipenem, longer stay in ICU, pneumonia and diabetes mellitus [10]. Cases of community acquisition have been described in situations of chronic obstructive pulmonary disease (COPD), diabetes, alcoholism and cancer [11]. It has great capacity to acquire and accumulate

resistance genes from other GNB via plasmids/transposons, with low permeability for many antibiotics, constitutive ejection pumps, production of beta-lactamases and so on.

*Klebsiella pneumoniae* (Kp) contaminates the medical material although its main reservoir is the digestive tract and the hands of the health care personnel from where it can give rise to epidemic outbreaks. Its main mechanism of resistance is the production of beta-lactamases. The genes that encode them are transmitted by plasmids, which contribute to their rapid diffusion among other GNB.

MRSA shows resistance to methicillin by means of a protein encoded in the mecA gene and transported in the chromosomal cassette SCCmec. The frequent use of vancomycin has led to the emergence of strains with intermediate or complete resistance to vancomycin by acquisition of the gene through a plasmid. They currently constitute up to 50% of Staphylococcus infections.

### 1.6. Factors that predispose to infections by MRB

Certain elements as advanced age, functional dependence, cognitive deterioration and comorbidities, prolonged hospital stays, contact with personnel sanitary, intravascular catheters, bladder catheterization, previous antibiotic treatment, and so on, contribute to an increased selective pressure (leading to the emergence of MRB) and increased colonization pressure (through an ineffective environmental containment) [11].

### 1.7. Consequences of infection by MRB

The prognosis of MRB infections is not good, with an increase in hospital stay, mortality and economic costs [12]. These types of infections are usually resistant to empirical therapies, which implies a delay in starting the correct antibiotic treatment. Also derived from this, the use of second line treatment with lower bactericidal capacity and less favorable pharmodynamic/pharmacokinetic profile contributes to a higher incidence of adverse events. At times, a greater virulence of these germs has been described.

### 1.8. Colonization and infection

The difference between these two terms lies in the simple presence (colonization) or clinical involvement (infection). The oropharynx is colonized early by hospital flora, especially GNB, in critically ill patients. The risk of colonization increases with hospital stay and severity. In the same way, the administration of antibiotics systemically increases the risk of acquiring the carrier state. Patients with APACHE II greater than 20 are usually carriers of abnormal flora such as GNB and MRSA. The passage from colonization to infective germs is defined by the rupture of the natural defense mechanisms (neutropenia, immunosuppression), the pathogenicity of the germ itself, alteration of the intestinal flora by antibiotic therapy previously administered. Altered mechanisms of clearance of germs are suggested. A necessary factor for the development of the infection is the overgrowth; 20–40% of carrier patients develop an infection, so those carriers must be actively identified when we want to control an outbreak of infection by resistant flora.

### 1.9. Exogenous-endogenous infections in the ICU

Infections can be classified according to origin and carrier status:

- Exogenous: nonpreceded by digestive colonization. The infective flora is endemic to the ICU. It constitutes 10–15% of the infections acquired in critical care.

- Endogenous: preceded by colonization of the digestive system by potentially pathogenic germs (PPG). It is endogenous primary if the patient already has them at the time of admission. It is usually precocious and represents 50% of registered infections. The endogenous secondary is caused by germs acquired in the ICU and colonizes the patient before causing the infection. They represent 35–40% of infections acquired in critical care.

The multimodal prevention of nosocomial pneumonia is based on these concepts. Primary endogenous pneumonias can be prevented with a short course of antibiotics such as cefotaxima that eliminates the colonizing germs of the oropharynx and upper respiratory tract of the carriers. Endogenous pneumonia is treated with the prevention of the carrier state with enteral antibiotics (PPG will not be able to adhere the coated mucosa of antibiotics). Exogenous pneumonia is prevented with hygienic measures.

### 1.10. Mechanisms of appearance and extension of resistance

The main responsible for the emergence and extension of resistance are the indiscriminate use of antibiotics and the transmission of resistant microorganism between humans (or between human and environment). The antibiotics exert a selective ecological pressure on the bacteria, thus promoting the appearance of resistance germs. Inadequate practices of prevention of the infection along with inadequate hygienic measures will favor the extension of the bacteria. The strategies to avoid these phenomena are aimed at a better use of antibiotics (reducing the selective pressure) and optimizing the infection control measures (reducing the colonization pressure) [13, 14].

Some measures aimed at a rational use of antibiotics are the following:

- Evaluation committees: formed by clinicians, pharmacists and microbiologists; pursue the effective and safe use of antimicrobials, evaluate and guide decision making; and implement educational programs to improve the use of antibiotics;

- implementation of clinical guidelines and protocols to promote the proper use of antibiotics;

- to use a form with pre-authorization for broad-spectrum antibiotics (non-specific restriction);

- preferred use of limited spectrum antibiotics (first-generation cephalosporin);

- personalized audit (mandatory consultation with infectious disease specialists to improve the appropriateness of antibiotic therapy and to reduce the use of broad spectrum antibiotics);

- to use predictive scores for MRB infections can be useful to minimize both the time to initiate appropriate antibiotic treatment and the unnecessary use of broad spectrum antibiotics.

While some measures of patient-patient transmission control are:

- hand washing;

- contact isolation measures (very important in case of MRSA, ERV and germs producers of ESBL), even grouping the colonized/infected patients (cohorting) and having staff exclusively dedicated to the care of these infectious patients;

- the use of universal contact precautions is not clear in all patients admitted to ICU;

- cutaneous decolonization/daily bath with chlorhexidine to colonized/infected patients (despite the limitations of the current studies) [15];

- decolonization of the upper respiratory tract and gastrointestinal tract. Several options: oropharyngeal decontamination with antiseptics (chlorhexidine); selective oropharyngeal decontamination (with nonabsorbable antibiotics applied to the oropharynx); and selective digestive decontamination (with nonabsorbable antibiotics applied to the oropharynx with intravenous antibiotics);

- surveillance of early infections by MRB (for early identification of these germs, control of outbreaks—imited in time—and situations of endemic increase of isolation);

- to implement strategies of infection prevention in relation to invasive devices (reduce the use of central venous catheters, bladder catheters, orotracheal tubes, etc);

- to regulate and monitor the process of cleaning, disinfection and environmental sterilization.

### 1.11. Proper antibiotic treatment

The evolution of an infectious process depends on the characteristics of the initial focus, the hemodynamic parameters, host factors, the responsible pathogen, in vitro antibiotic susceptibility tests and the precocity of the appropriate antibiotic treatment. The use of antibiotics is, at the same time, part of the problem and the solution when we talk about antibiotic resistance. Unfortunately, the emergence of resistance is faster than the creation of new antibiotics by the pharmaceutical industry. In general, the solution involves a global reduction in the consumption of antibiotics, although it is necessary to implement control programs aimed at rationalizing their use.

A frequently forgotten fact is that the majority of antibiotic consumption is done at the extra-hospital level (Primary Care and food industry) [16]; it is necessary to regulate its use. Up to 50% of antibiotics prescribed at the hospital level are unnecessary, many of them are broad spectrum. The inadequate use of antibiotics increases the mortality of patients with severe sepsis, subjects them to unnecessary adverse effects and generates unjustified expenses. On the other hand, it is of vital importance to define the role of prophylactic antibiotic treatment and also differentiate the systemic inflammatory response syndrome of any cause from a real infectious process.

The loss of sensitivity to antibiotics is to be solved with several strategies: to speed up the development of new antimicrobials—the initiative "10 × 20" of the IDSA; 10 new antimicrobians available on 2020; to improve the mechanisms of infection control in health centers; and

to optimize the use of current antibiotics with the intention of extending their useful life. An adequate administration of antibiotics should be based on the following principles:

- early start (associated with microbiological cultures);

- proper choice of antibiotic: based on local ecology and habitual patterns of resistance;

- suitable doses, based on pharmacokinetic and pharmacodynamics data, taking into account that in critical patients the increase in volume of distribution, cardiac output and glomerular filtration requires the administration of doses that could be above the usual doses (currently available antibiotics rarely cause serious adverse effects);

- evaluate the need to maintain the started treatment: to remove unnecessary antibiotics by culture results, and if possible, to narrow the spectrum (de-escalation);

- adequate duration of antimicrobial treatment (usually too long due to the absence of evidence of optimal duration and for fear of suspending it if the evolution of the patient is good).

Different strategies have been described and tested to avoid resistance to antibiotic. Rotation consists of restricting in an established way an antibiotic or a class of antibiotics during a certain period of time, to reintroduce it later; the aim is to reduce the selective pressure exerted on the microbial flora and to minimize the appearance of resistance to rotated antibiotics. Cycling is to prescribe antibiotics according to a pre-established a priori sequence. In scheduling, an antibiotic or antibiotic class is replaced by another antibiotic or class with a comparable antimicrobial spectrum; there is change to another antimicrobial without returning to the initial agent. In rotation, there is a circular pattern. The usefulness of these strategies is theoretical. Periodic modifications would limit the generation of resistances by avoiding prolonged exposures to the same antimicrobial agent; the restriction of an antibiotic can result in the compensatory potentiation of the use of other unrestrained agents, with a later increase of resistance to these second agents. Also, the elimination for the selective pressure by an antibiotic when withdrawing its use does not imply the eradication of the genetic material responsible of the resistance. Despite the theoretical benefits of these strategies, their results are contradictory, and none of them have showed real benefit so far [17].

### 1.12. Epidemiological surveillance: multimodal prevention program

Epidemiological surveillance consists of the systematic collection, analysis and interpretation of data about a problem related to public health. The implementation of multimodal prevention programs must have the following elements: identification of problems, implementation plan, involvement of managers, record of compliance with objectives and, finally, the analysis of obstacles that may arise. An essential aspect of these programs is learning: the absence of adherence to the measures of the program due to lack of information or insufficient learning time should be avoided.

The antimicrobial stewardship programs bring together specialists in infectious diseases, clinical pharmacologists, clinical microbiologists, epidemiologists and other, sometimes also intensivists, all of them gathered for the purpose of an adequate prescription of antibiotics. But this is just one aspect of a complex problem like antibiotic resistance.

The 12 steps described by the CDC to prevent antibiotic resistance are the following:

- prevention of the infection:

- vaccine administration;

- removal the catheters (as soon as possible);

- effective diagnosis and treatment of the infection:

- analyze the sensitivity of the germ and to adapt the treatment to the pathogen;

- discuss with experts;

- appropriate use of antimicrobials:

- antibiotic control;

- knowledge of local microbiological data;

- treat the infection, not the colonization or the contamination;

- know how to refuse vancomycin;

- stop antibiotic treatment if patient has healed (propose the reduction of antibiotic treatment according to the clinical situation of the patient);

- prevention of the transmission:

- isolate the pathogen;

- break the chain of infection.


## 2. Resistance Zero (RZ) project

The Spanish Society of Intensive Care (SEMICYUC) has developed several projects with the aim of reducing infectious events (nosocomial infections): Bacteremia Zero (BZ) (catheter-related bacteremia) and Pneumonia Zero (NZ) (pneumonia associated with mechanical ventilation). After the implementation of these projects, a sustained decrease in the rate of such infections, and globally nosocomial infections has been achieved (**Figure 1**). It has been described that, surprisingly, the rate of pneumonia associated with mechanical ventilation began to decrease with the start of the BZ Project.

The last project carried out is Resistance Zero (RZ). Its objectives are:

- Primary: reduce by 20% the appearance of one or more MRBs of Nosocomial origin that are identified during their admission in ICU;

- Secondary: describe the MRB map in spanish ICUs, differentiating those identified at the time of admission to the ICU and those that appear after 48 h of stay; promote and reinforce the safety culture in them; and create a network of UCIs, through the autonomous communities, that apply safe practices of demonstrated effectiveness.

The aim of the project is to minimize the three factors that influence the appearance of MRB in critical patients: the adequate prescription of antibiotics, the early detection of MRB and
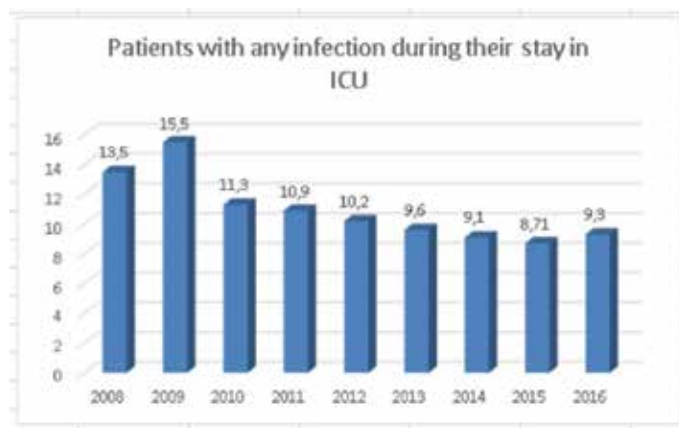
**Figure 1.** Decrease of acquired in ICU infection rate (patients with acquired in ICU infections for every 100 patients admitted to the ICU) during the different zero projects. Start of BZ 2009: Start of NZ 2011; start of Resistance Zero 2014.

the prevention of its spread/cross colonization, and the elimination of reservoirs. The MRBs in follow-up are: MRSA, VRE, Enterobacteria resistant to third generation cephalosporins, especially the ESBL producers, and those resistant to carbapenems, especially the carbapenemase producers; *P. aeruginosa* resistant to >= 3 families of antibiotics including: carbapenems, cephalosporins, piperaziline/tazobactam, fluoroquinolones, aminoglycosides, colistin; and *Acinetobacter baumannii* resistant to carbapenems.

The recommendations of the project are:

1. Identify in each ICU at least one intensivist physician responsible for the control of antibiotics, with experience in surveillance and infection control and in the management of antibiotics. Systematically evaluate the use of antibiotics in ICUs and advise physicians responsible for patients with the intention of assessing reasons for prescription (indication), assessing choice and correct administration (dose, interval, duration) and possibility of withdrawal or adjustment.

2. Administer antibiotics empirically active against MRB only in infections with systemic response (severe sepsis, septic shock (SS)), and high suspicion of being MRB based on present risk factors and local epidemiology. In other cases, it is recommended to use lower spectrum antibiotics and/or wait for microbiology results to start antibiotics directed to MRB (carbapenems, colistin, tigecycline, glycopeptides, daptomycin, linezolid). In critical surgical patients with infection data but without sepsis/SS, the start of antibiotic treatment can be delayed until microbiological confirmation, without this implying an increase in mortality or stay in the ICU.

3. Designate a nurse as a project reference and responsible for the control of precautions directed to preventing the transmission of MRB. Ensure the effective implementation of the handwashing strategy, and dispose of an alcohol-based preparation dispenser in each bed.

4. Perform an active search for the presence of MRB in all patients at the time of admission to the ICU, and at least once a week throughout their stay. The type and number of samples will be chosen according to the local epidemiology, and at a minimum, they will include

nasal, rectal and oropharyngeal swabs (tracheal aspirate in intubated patients); in addition, you can take other samples to control possible reservoirs (infections, skin ulcers, etc). The samples will be processed to identify the MRBs recommended by the local epidemiology, according to Microbiology and the infection control teams of each hospital.

5. At the time of admission of each patient in ICU, a checklist that includes several items (hospital admission>5 days in the previous 3 months, institutionalized-prison, social health centers, nursing homes-, colonized or infected by MRB) will be completed., antibiotics> = 7 days in the previous month -especially with third and fourth generation cephalosoporins, quinolones and carbapenemics-, chronic renal failure undergoing hemodialysis or chronic ambulatory peritoneal dialysis, and chronic pathology with a high incidence of MRB colonization/infection-cystic fibrosis, bronchiectasis, chronic ulcers-) with the objective of identifying those patients with high risk of being carriers of MRB. In patients with one or more risk factors, preventive contact precautions will be applied, and surveillance culture samples will be collected.

6. Control compliance with the different types of precautions that should be applied: standard, or based on transmission mechanisms (isolation). The precautions will vary according to the identified MRB and its transmission mechanism (drops, air, and contact). They are mandatory standards for all health personnel and for the families of the patient. Nursing empowerment must be recognized to control strict compliance. The presence of necessary material for its application must also be facilitated. Contact isolation should be practiced with the use of a coat and gloves before contacting the patient, and removing them before leaving the patient's environment (for a single use).

7. Have an updated protocol for daily and terminal cleaning of rooms occupied by patients with MRB. Several aspects must be agreed with the cleaning and Preventive Medicine teams of the hospital: the cleaning method (method, frequency, products, etc.) according to the type of surface and the fixed structures present, including the beds.

8. Elaborate a document for cleaning the clinical material and scanning devices in the ICU, commonly used in hospitalized patients, assessing whether cleaning, disinfection or sterilization is necessary. The importance of cleaning the sanitary material (fondendoscopes, fiberoptic bronchoscopes, etc.) and nonsanitary (computer keyboards, landline and mobile phones, keys, etc.) usually used in the ICU should be made aware. It is the responsibility of each worker to clean and disinfect appliances for personal use.

9. Include products containing chlorhexidine (4% soaps or other products impregnated with 2%) in the daily hygiene of patients colonized/infected with MRB, in addition to the obvious need for cleaning to eliminate organic waste.

10. Given the suspicion of an epidemic outbreak, it is recommended to typify at a molecular level the causative microorganism to know the clone responsible for the outbreak and its traceability. Studies of outbreaks based on phenotypic characteristics (antigenic, metabolic or antibiotic resistance properties) are insufficient to establish conclusive differences or similarities between microorganisms. The molecular typing allows us to know the transmission mechanisms of the pathogen to establish measures that prevent its dissemination. The centers that do not have means can submit the microbiological samples to the Resistance Vigilance Program of the National Microbiology Center of the Carlos III Health Institute (Madrid).

As additional recommendations, hand hygiene is very important, with the use of hydroalcoholic solution by health personnel before and after patient care. It is the most effective measure for the transmission of germs. Its purpose is to prevent the transmission of microorganisms in a bidirectional way between professionals and patients, besides protecting the care environment of pathogenic microorganisms. The priority method to perform hand hygiene in the absence of organic matter or visible dirt is the friction with alcohol-based products. They will not be used in case of contact with patients/surfaces contaminated with spores (C difficile). Gloves should be worn in several situations: when handling blood or body fluids, mucous membranes or non-intact skin, when transporting or touching surfaces stained with blood, liquids or body fluids, or performing any procedure of blood extraction or parenteral treatment. They must be changed if they are broken or contaminated, between one patient and another, and between procedures in the same patient. The misuse of gloves increases the risk of pathogen transmission, and its use never substitutes for hand hygiene.

The indicators used in the RZ project are:

- Rates of patients with one or more BMR acquired in ICU: number of patients admitted to the ICU with 1 or more MRBs identified after 48 h of admission (and up to 48 h after discharge from the ICU) for 1000 days of stay in ICU, or by 100 patients admitted. MRBs are evaluated in clinical samples (infections or colonizations) and in surveillance samples, but not in environmental samples.

- Rate of days free of antibiotics: number of days—patient who does not receive systemic antibiotics for 1000 days of ICU stay. All systemic antibiotics are included regardless of the reason for their use.

- Rate of antibiotic use in infections acquired in ICU: number of days - patient with systemic antibiotic treatment for infections acquired in ICU, for 1000 days of ICU stay.

The project is complex and flexible, and adapts to the reality of each hospital. It is also contemplated to apply an integral security plan that seeks to promote and strengthen the safety culture in the daily work in the ICUs. Health professionals who provide critical care to the critically ill patients must be aware of the security risks of our units. The culture in general safety of the unit must be evaluated. We must work proactively on the potential risks of critical patient care, and propose recommendations based on daily practice that tries to minimize them. The notification of errors should be encouraged, and a goal of improvement should be proposed over time, with follow-up of proposed measures to achieve it. We have developed daily checklist tools that assess the safety of the patient on a daily basis in the different spheres of their management, and even a list of daily objectives—need of tubes/catheters, assessing whether parenteral medication can be suspended or passed to oral route, possibility of discharge from the ICU, and so on.

This project has preceded and promoted the creation of a new National System for the Surveillance of Infection Related to Health Care in Spain, in agreement with the Ministry of Health.

## 3. European data. ECDC

Data on infections associated with healthcare acquired in ICU are assessed by the ECDC. Recent data (2015) [1, 2] show that 8.3% of patients who remain in the ICU for more than
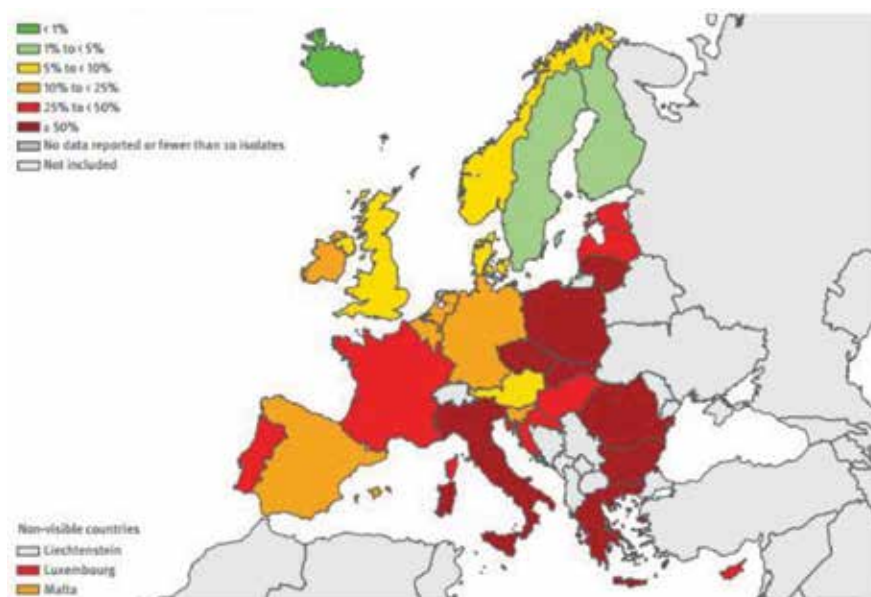
**Figure 2.** North-south and west-east gradient of % resistance of *K. pneumoniae* to third generation cephalosporins.

48 h develop at least one infection (pneumonia, bacteremia or urinary tract infection). The most frequent causal germs are *P. aeruginosa* (pneumonia), *Staphylococcus* spp. coagulase-negative (bacteremia) and *Escherichia coli* (urinary tract infections). On average, 23.1% of *S. aureus* are MRSA; 3.4% of Enterococci are VRE. Resistance to third generation penicillin is described in variable percentages in E coli (20%), Klebsiella (43%) and Enterobacter (42%); resistance to carbapenems is also noticeable in Klebsiella (11%), *Pseudomonas aeruginosa* (24%) and *Acinetobacter baumannii* (69% of averages). In a report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) of 2016 [2], the main surveillance system in the European Union on bacteria that can cause serious infections, broad variations are described in relation to bacterial species, antimicrobial group and geographical region. For many combinations of bacterial species (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter*, *S. aureus*, *Enterococcus*)—resistance to antimicrobial groups, there is a growing gradient from north to south, and from west to east, perhaps in relation to variations in the use of antimicrobials, infection prevention and control practices, and differences in diagnosis and healthcare utilization patterns between countries [18]. Overall, there seems to be a slowly increasing resistance over time (in the 2013–2016 interval) of E coli resistant to one of the three key antimicrobial groups (fluoroquinolones, third generation cephalosporins and aminoglycosides), with a tendency to stabilize the percentage of *K. pneumoniae* resistances (**Figure 2**).

## 4. Global data in Spain: ENVIN study: RZ project

The national study of nosocomial infection surveillance (ENVIN) represents the effort maintained over time (since 1994) to know and reduce the prevalence of nosocomial infection

in ICUs. It describes nosocomial infections (NI) acquired in ICUs associated with invasive instrumentation. The data are collected mainly during the second quarter of the year (few units carry out the project throughout the year). The more frequent NI in the ICU are urinary infections associated with urinary catheter (31.87%), followed by ventilation-associated pneumonia (29.97%) and bacteremia (catheter-associated bacteriemia in 11.31%). In recent years, there has been a relative increase in the former ones and a decrease in the latter. The most frequently isolated germs in ICU infections (excluding bacteremia from other foci) are: *E. coli* (14.1%), *P. aeruginosa* (12.9%), *K. pneumoniae* (9.8%), *S. epidermidis* (8.2%), *S. aureus* (4.9%), *C. albicans* (4.8%), *E. cloacae* (3.5%), *S. marcescens* (2.7%), and so on. The type of reported patients is variable: medical (44%), 19.5% of surgeries scheduled, 10.3% of urgent surgeries and 19.8% of coronary patients. The extrinsic risk factors for nosocomial infections are: antibiotics before admission (21.1%), antibiotic treatment in ICU (64%), surgery in 30 days before (32.8%), urgent surgery during their stay in ICU (10.2%), central venous catheter (63.9%), mechanical ventilation (42.4%), bladder catheter (76.4%), parenteral nutrition (8.3%), and so on.

The implementation of the RZ project is more complex than the previous programs. It involves the collaboration of more staff and services, so the number of participating ICUs has been lower (of>190 in the first two projects, compared to 103 in RZ). In the following graphs, the evolution of the different indicators collected in the project is reviewed.

The evolution by quarters of the frequency of colonization/infection of patients with MRB, per 100 patients admitted, throughout the development of the RZ project is observed in **Figure 3**, with an ascending tendency with peaks coinciding with the collection periods of data from the ENVIN project (second quarter of each year). The average value throughout the project is 6.23 patients per 100 admissions. The colonization/infection plot for 1000 stays is similar.

Throughout the RZ project, there is an increase in the isolation of germs at the admission (acquisition prior to admission to the ICU) versus isolation during their stay (discrete decrease),
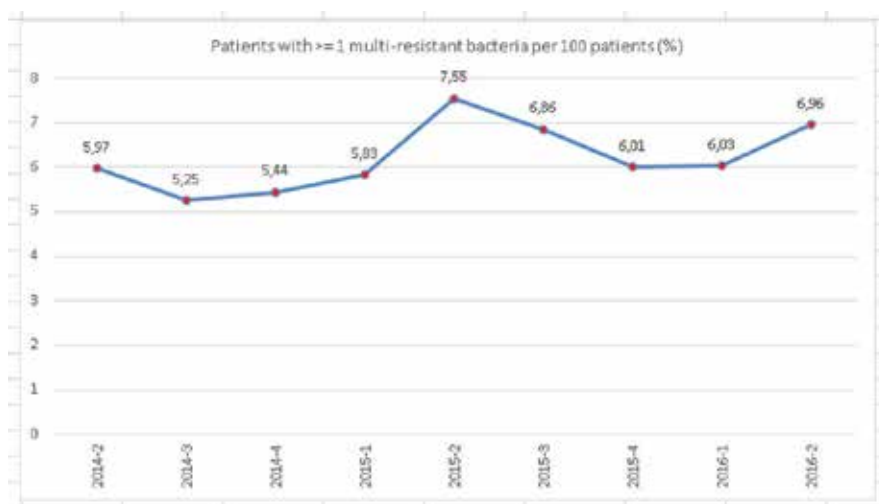


**Figure 3.** Temporal variation of the rate of MRB colonization/infection in ICU.

taking into account colonizations and infections (**Figure 4**). The average value during the project is 3.84 patients% (previous) and 2.60% (during), with an increase of the previous ones of 26% and a decrease of those acquired during the ICU admission of 16.7%.

In relation to the germs acquired in the ICU, there was a slight increase in colonization (5%) and a significant decrease in MRB infections (45%) (**Figure 5**), with average values of 1.75% patients colonized and 1.09% of infected.

**Figure 1** (see above) and the following ones (**Figures 6–8**) show the tendencies initiated with the BZ and NZ projects of descent of patients admitted to the ICU with an infection (up to 8.7%, **Figure 1**), of reducing the use of antibiotics (up to 19.5% of patients, **Figure 6**), of reducing the days of antibiotic treatment (DOT, up to 109.7 per 1000 stays, **Figure 7**) and increasing days without antibiotic treatment (up to 40%, **Figure 8**). A rate of 2.15 antibiotics per patient with antibiotic treatment is described in 2016.

MRB colonization-infection rates change in successive years (**Figure 9**), with significant increases in enterobacteria carrying ESBL and carbapenemases and decrease in *A. baumannii, P. aeruginosa* and MRSA.

We can distinguish between the isolation of germs upon admission and during their stay, which can allow us to distinguish the predominant MRB germs that the patient "brings" to the ICU with those that he/she "acquires" during his stay. **Figure 10** shows that Acinetobacter infections appear mostly during their stay, against infections by ESBL-producing germs that are mostly present at admission.

**Figures 11** and **12** show an important variability in the different autonomous communities, both in the MRB isolation rate (global of 6.23 per 100 patients) and in the isolated MRB types, for a total of 3195 isolated MRBs.
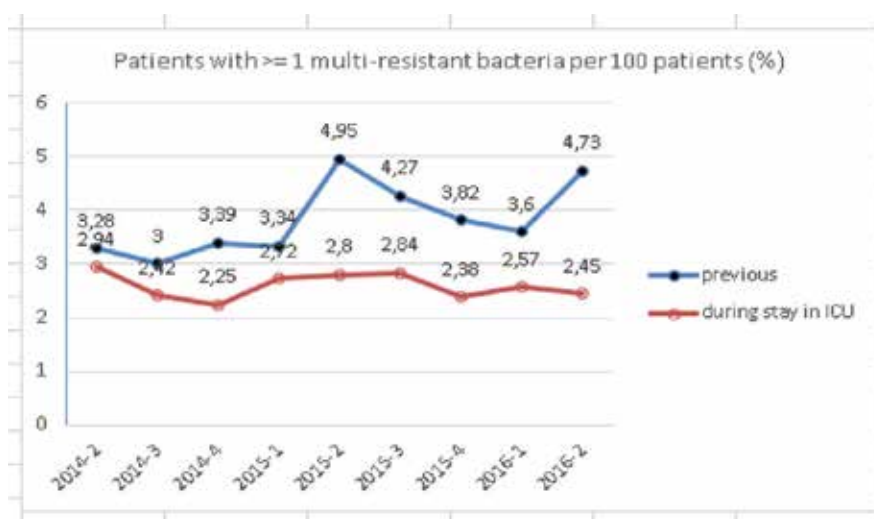


**Figure 4.** Evolution of BMR isolates prior to admission to the ICU and during admission.
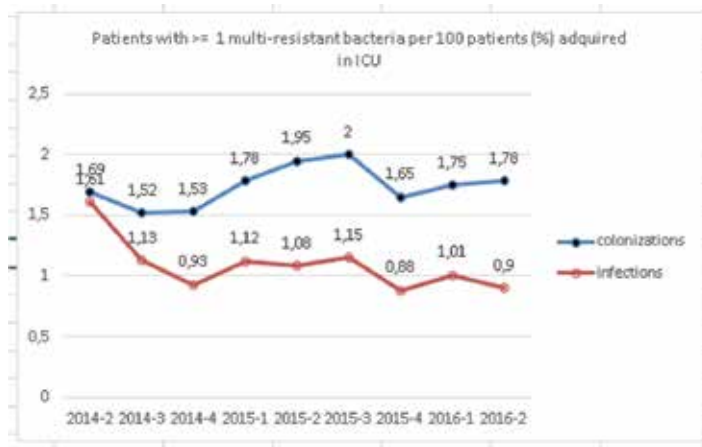
**Figure 5.** Evolution of colonized and infected patients during their stay in the ICU.
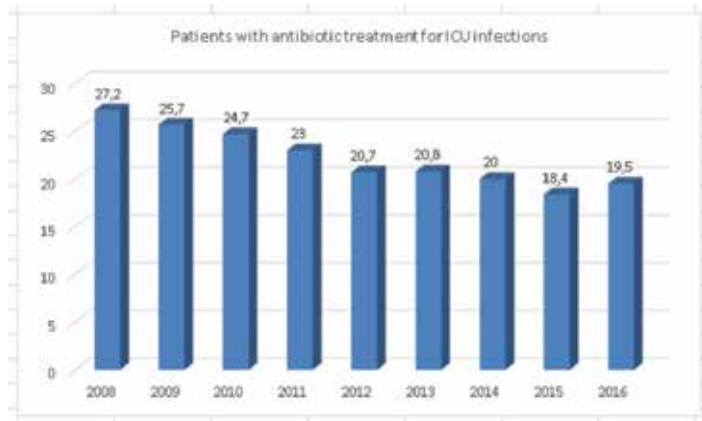


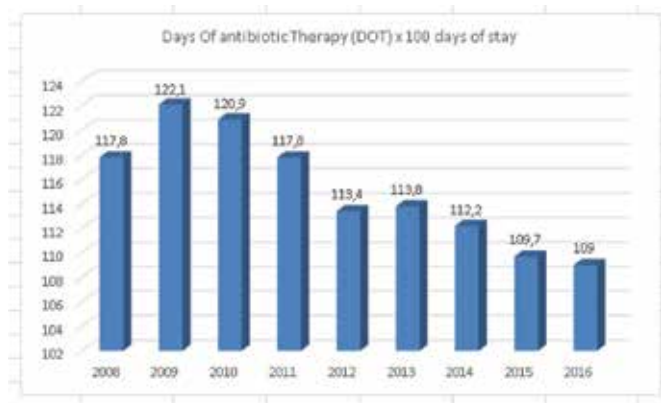**Figure 6.** Reduction in the use of antibiotics over time.



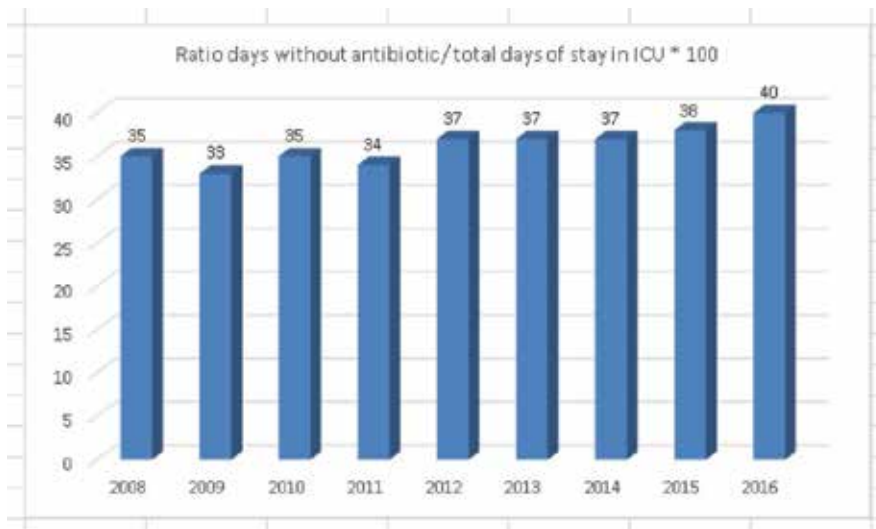**Figure 7.** Reduction in the use of days of antibiotic treatment (DOT) for 100 stays in the recent years.

**Figure 8.** Increase in the number of days in the ICU without antibiotic treatment over the years.
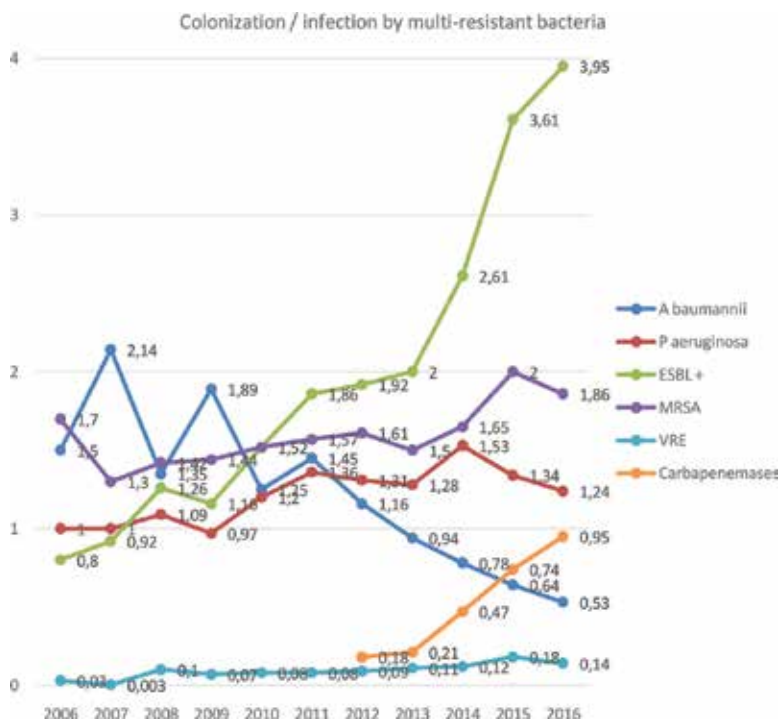


**Figure 9.** Infection/colonization by MRB. ENVIN study in the interval 2006–2016.
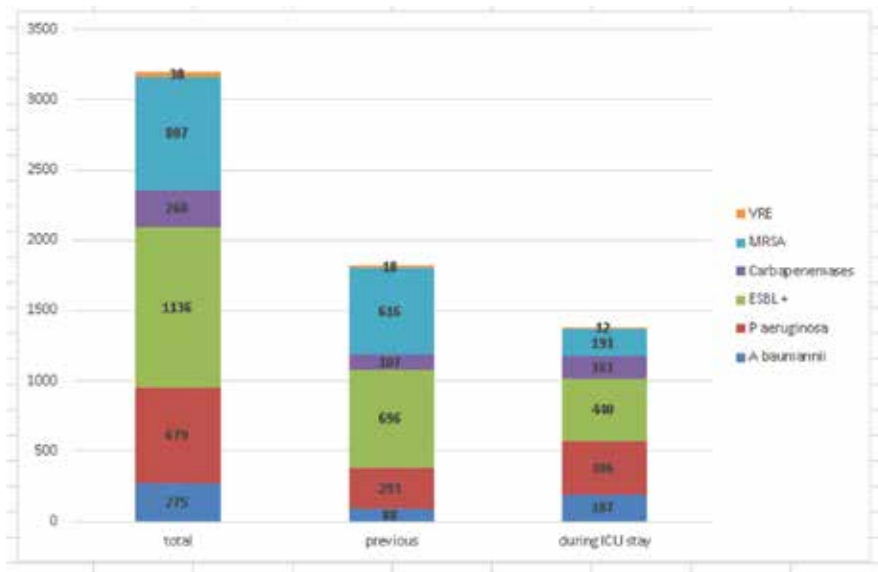
**Figure 10.** Isolation of MR germs in the RZ period globally, upon admission and during their stay in the ICU.
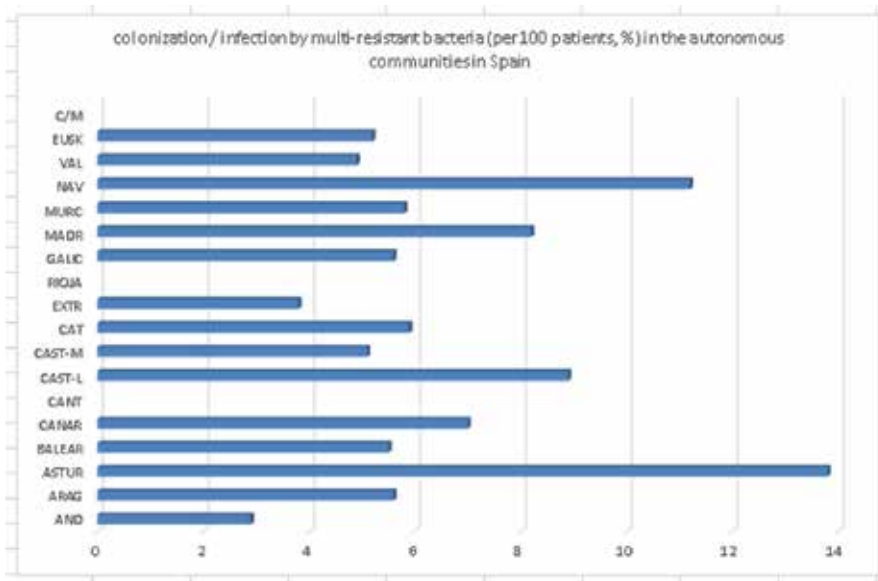


**Figure 11.** Isolation rate in the different autonomous communities. AND Andalucia, ARAG Aragón, ASTUR Asturias, BALEAR Balearic Islands, CANAR Canary Islands, CAST-L Castilla-León, CAST-M Castilla-La Mancha, CAT Catalonia, EXTR Extremadura, RIOJA La RIOJA, GALIC Galicia, MADR Madrid, MURC Murcia,NAV Navarra, VAL Valencian community, EUSK Euskadi, C/M Ceuta/Melilla.

multi-resistant bacteria isolates in autonomous communities of Spain
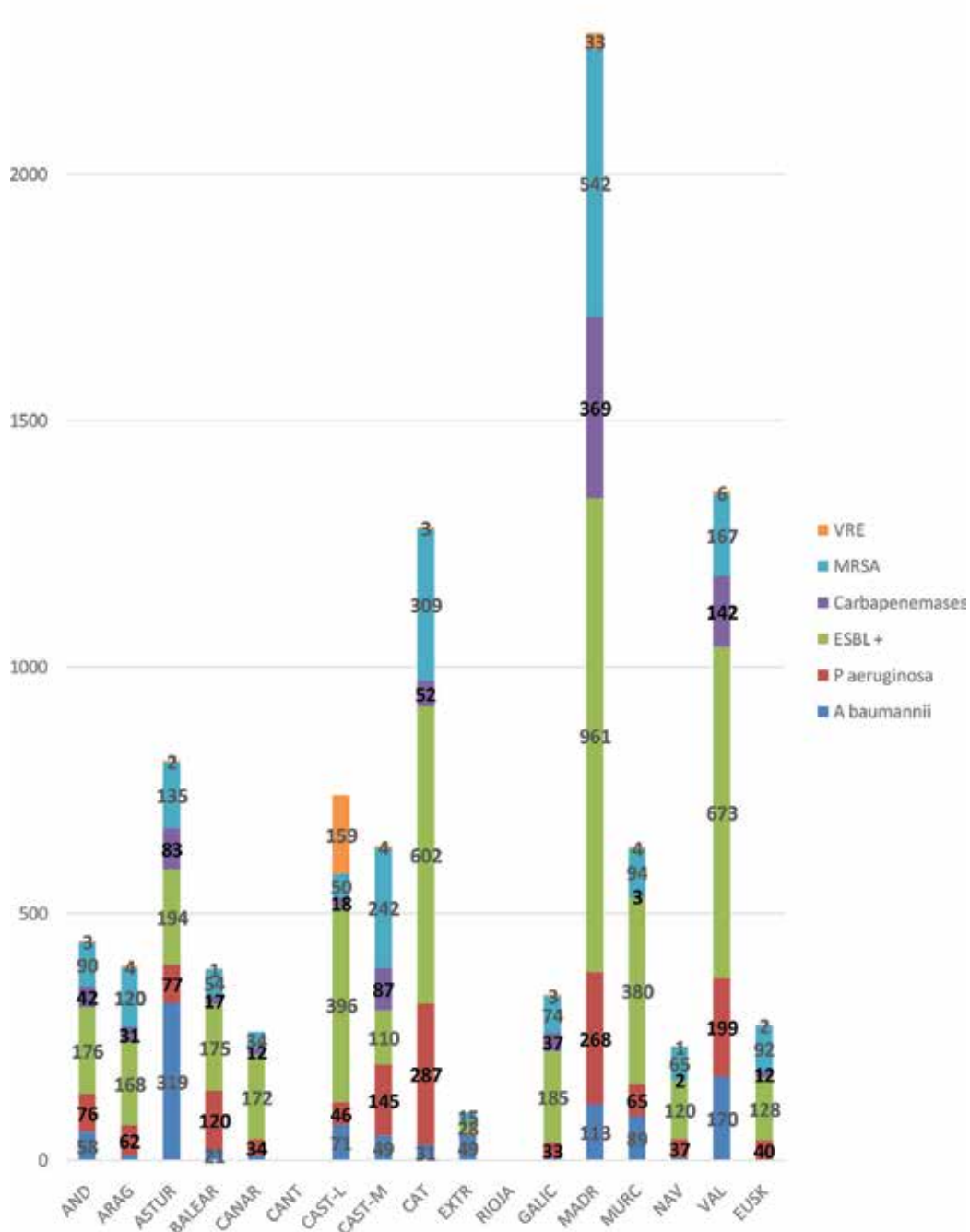


**Figure 12.** Heterogeneity of MRB isolates, counting colonizations and infections, during the period of RZ study. In most autonomous communities, the most frequent type of MRB is ESBL producing GNB. The presence of *A. baumannii* has become much less frequent, except in Extremadura and Asturias. In the Canary Islands, there are 0 VRE isolates; in Extremadura, there are zero isolates of VRE, one isolation of carbapenemase producing germ and three isolates of *P. aeruginosa*; there are few isolates of *A. baumannii* in Aragón [9], Canary Islands [8], Galicia [3] and Navarra [5]; and finally there is no isolation (0) of *A. baumannii* in Euskadi.

## 5. Data of the ICU of the hospital of Sagunto

Our unit starts the data collection in the ENVIN project the same year of its beginning (1994). We started the RZ project in April 2014, and until now (January 2018) have followed the guidelines of the RZ project in the prevention and management of patients with MRB. We reported 195 isolates in 179 patients for 46 months, with 1966 admissions and a rate of 9.1 patients with MRB/100 admissions (**Figure 13**).

In our unit, a high prevalence of *A. baumannii* was initially observed, without a clear seasonal profile. Over time, there is a decrease in *A. baumannii* and an increase in the ESBL carrier



**Figure 13.** Occurrence of MRB in our ICU Fromm the beginning of RZ project until February 2018. Acinetobacter supposes globally a 25% of isolates, with a rate of 50% of ESBL producer germs.

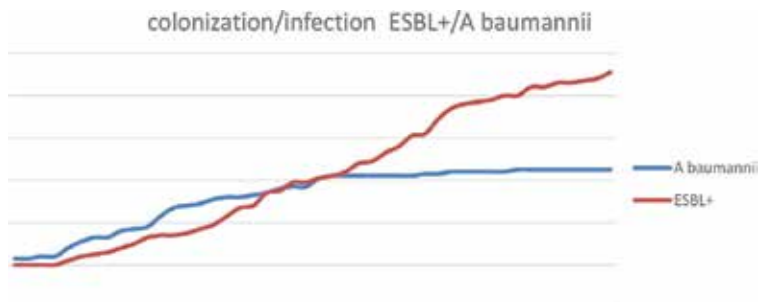**Figure 14.** Accumulated frequency of colonized and infected patients by *A. baumannii* and ESBL producer germs.
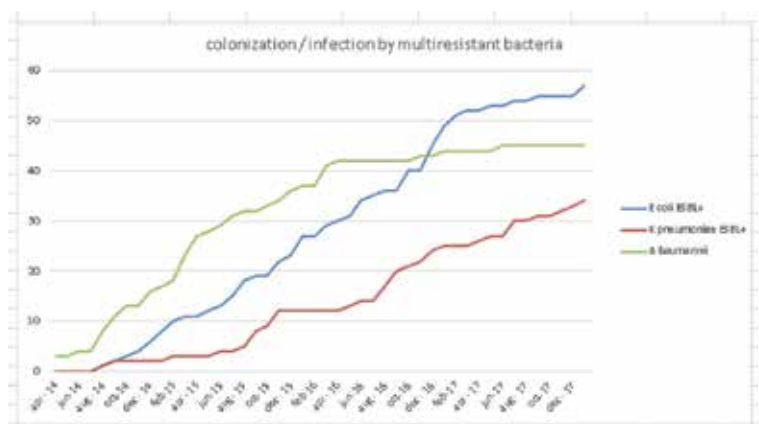


**Figure 15.** Accumulated frequency of colonized and infected patients by the most frequently isolated germs in the ICU of the hospital of Sagunto.



**Figure 16.** Indicators of the RZ project at the local (hospital of Sagunto), regional (Valencian community) and national (Spain) levels.

**Relación de Bacterias Multirresistentes al ingreso y durante el ingreso**

| UNIDAD | N | % | COMUNIDAD VALENCIANA | N | % | NACIONAL | N | % |
|---|---|---|---|---|---|---|---|---|
| SARM (MRSA) | 12 | 10.08 | SARM (MRSA) | 433 | 21.46 | SARM (MRSA) | 3230 | 21.20 |
| Enterococo resistente Vancomicina | 1 | 0.84 | Enterococo resistente Vancomicina | 9 | 0.45 | Enterococo resistente Vancomicina | 273 | 1.79 |
| Pseudomonas multirresistente | 13 | 10.92 | Pseudomonas multirresistente | 337 | 16.70 | Pseudomonas multirresistente | 2560 | 16.80 |
| Acinetobacter R-Imipenem | 42 | 35.29 | Acinetobacter R-Imipenem | 212 | 10.51 | Acinetobacter R-Imipenem | 1397 | 9.17 |
| Enterobacteria - BLEE | 51 | 42.86 | Enterobacteria - BLEE | 859 | 42.57 | Enterobacteria - BLEE | 6396 | 41.98 |
| BGN - Carbapenemasa | 0 | 0.00 | BGN - Carbapenemasa | 168 | 8.33 | BGN - Carbapenemasa | 1380 | 9.06 |
| TOTAL | 119 | | TOTAL | 2018 | | TOTAL | 15236 | |

**Relación de Bacterias Multirresistentes durante el ingreso incluyendo colonización e infección**

| UNIDAD | N | % | COMUNIDAD VALENCIANA | N | % | NACIONAL | N | % |
|---|---|---|---|---|---|---|---|---|
| SARM (MRSA) | 0 | 0.00 | SARM (MRSA) | 113 | 11.36 | SARM (MRSA) | 721 | 11.46 |
| Enterococo resistente Vancomicina | 0 | 0.00 | Enterococo resistente Vancomicina | 3 | 0.30 | Enterococo resistente Vancomicina | 114 | 1.79 |
| Pseudomonas multirresistente | 3 | 10.00 | Pseudomonas multirresistente | 217 | 21.81 | Pseudomonas multirresistente | 1472 | 23.08 |
| Acinetobacter R-Imipenem | 19 | 63.33 | Acinetobacter R-Imipenem | 139 | 13.97 | Acinetobacter R-Imipenem | 948 | 14.86 |
| Enterobacteria - BLEE | 8 | 26.67 | Enterobacteria - BLEE | 403 | 40.50 | Enterobacteria - BLEE | 2365 | 37.08 |
| BGN - Carbapenemasa | 0 | 0.00 | BGN - Carbapenemasa | 120 | 12.06 | BGN - Carbapenemasa | 748 | 11.73 |
| TOTAL | 30 | | TOTAL | 995 | | TOTAL | 6378 | |

**Relación de Bacterias Multirresistentes durante el ingreso solo infección**

| UNIDAD | N | % | COMUNIDAD VALENCIANA | N | % | NACIONAL | N | % |
|---|---|---|---|---|---|---|---|---|
| SARM (MRSA) | 0 | 0.00 | SARM (MRSA) | 18 | 6.19 | SARM (MRSA) | 316 | 11.72 |
| Enterococo resistente Vancomicina | 0 | 0.00 | Enterococo resistente Vancomicina | 2 | 0.69 | Enterococo resistente Vancomicina | 23 | 0.85 |
| Pseudomonas multirresistente | 1 | 33.33 | Pseudomonas multirresistente | 102 | 35.05 | Pseudomonas multirresistente | 830 | 30.79 |
| Acinetobacter R-Imipenem | 2 | 66.67 | Acinetobacter R-Imipenem | 46 | 15.81 | Acinetobacter R-Imipenem | 453 | 14.95 |
| Enterobacteria - BLEE | 0 | 0.00 | Enterobacteria - BLEE | 99 | 34.02 | Enterobacteria - BLEE | 881 | 32.68 |
| BGN - Carbapenemasa | 0 | 0.00 | BGN - Carbapenemasa | 24 | 8.25 | BGN - Carbapenemasa | 243 | 9.01 |
| TOTAL | 3 | | TOTAL | 291 | | TOTAL | 2696 | |

**Figure 17.** MRB isolated at admission and during their stay, such as colonization or infection, at the local, regional and national levels.

bacteria, and a slowly increasing incidence of MRSA and *P. aeruginosa* (**Figure 13**). Assessing the cumulative incidence, there is a catch-up of the ESBL + germs to the initially predominant Acinetobacter at the end of 2015–beginning of 2016 (**Figure 14**); if we separate the ESBL + germs, the highest cumulative frequency of E coli than of *A. baumannii* is observed at the end of 2016. In the last months also, the frequency of occurrence of *K. pneumoniae* is higher than that of *A. baumannii* (**Figure 15**).

During the RZ project, in our unit, 80 MRB were detected on admission and 26 during stay; this implies a global estimate, during the entire project period, of 6.29 patients with BMR at admission for every 100 admitted patients, and 2.04 patients with BMR during their stay in ICU per 100 patients admitted and 5.72 patients for 1000 stays. The income indicator is significantly higher than that of the Valencian Community (2.22%) and the national one (2.62%); and the indicators during their income are only slightly larger than the regional (1.87 and 4.28‰) and national (1.82 and 3.36‰) estimates (**Figure 16**). There have only been three nosocomial infections for BMR acquired in ICU during this RZ period, 1 for Pa and 2 for Ab, with a BMR infection rate acquired in ICU lower (0.24 per 100 patients admitted to ICU) than the regional (0.60%) and the national rates (0.79%).

The profile of germs is different: predominance in our unit of germs producing ESBL + (42.8%) and *A. baumannii* (35.3%), with a lower presence of *P. aeruginosa* (10.9%) and MRSA (10.1%). %); while at the regional and national level, the most common germs in decreasing order are Enterobacteria ESBL + (42.6% regional and 42% national), MRSA (21.5 and 21.2%), *P. aeruginosa* (16.7 and 16.8%), *A. baumannii* (10.5 and 9.2%) and GNB producers of carbapenemases (8.3 and 9.1%) (**Figure 17**).

## 6. Conclusions

The problem of multidrug resistance is serious. The loss of efficacy of antibiotics, within our current technified medicine, would limit procedures such as transplants, complex surgeries, the management of cancer patients, and so on. It is the responsibility of EVERYBODY to make an efficient use of antibiotics. We must remember that a large part of the use of these molecules is done at the industrial level, out of sanitary management.

The striking finding of the NORTH-SOUTH and WEST-EAST gradient of MRB isolates frequency can have several explanations: different policies of antibiotic use, environmental conditions (heat) that favors the persistence of certain germs in the hospital environment, variable culture of security within the hospital centers, and so on.

The RZ project, despite the difficulties in its development, shows efficacy in reducing MRB infections acquired in the ICU. It has been achieved up to 40% of the days in ICU without the use of antibiotics. The number of germs discovered at the time of admission is greater than during the stay in ICU. The MRBs that caused colonization acquired in ICU increased, while the infections acquired by BMR decreased. A great proportion of MRSA and ESBL among isolated microorganisms has been documented on admission, and germs producers of carbapenemases, *P. aeruginosa* and *A. baumannii* are more frequent during their stay in the ICU. There are important differences between autonomous communities; there may even be differences between different units of critics of the same hospital. The active search for MRB in patients at the time of admission has doubled its detection. The application of the recommended measures in RZ has achieved to reduce acquired MRB infections acquired up to 45%.

## Author details

Miguel Ángel García García[1]*, Alfonso Martínez Cornejo[1], David Arizo León[1] and María Ángeles Rosero Arenas[2]

*Address all correspondence to: mangelesymangel@gmail.com

1 Intensive Care Unit, Hospital de Sagunto, Valencia, Spain

2 Primary Care, Cheste, Valencia, Spain

## References

[1] US Department of Health and Human Services. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. 20th February, 2018. Available from: https://www.cdc.gov/drugresistance/threat-report-2013/index.html

[2] European Centre for Disease Prevention and Control. Healthcare–associated infections acquired in intensive care units. In: ECDC Annual Epidemiological Report for 2015.

Stockholm: ECDC; 2017. Available from: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-healthcare-associated-infections.pdf

[3] Fridkin SK, Welbel SF, Weinstein RA. Magnitude and prevention of nosocomial infections in the intensive care unit. Infectious Disease Clinics of North America. 1997;**11**:479

[4] Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. Journal of the American Medical Association. 2009;**302**:2323

[5] Hynes-Gay P, Lalla P, Leo M, et al. Understanding sepsis: From SIRS to septic shock. Dynamics (Pembroke, Ontario). 2002;**13**:17

[6] Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE. The Journal of Infectious Diseases. 2008;**197**:1079

[7] McDonald LC, Banerjee SN, Jarvis WR. Seasonal variation of acinetobacter infections: 1987-1996. Nosocomial Infections Surveillance System. Clinical Infectious Diseases. 1999;**29**:1133

[8] Sheppard FR, Keiser P, Craft DW, et al. The majority of US combat casualty soft-tissue wounds are not infected or colonized upon arrival or during treatment at a continental US military medical facility. American Journal of Surgery. 2010;**200**:489

[9] Siempos II, Vardakas KZ, Kyriakopoulos CE, et al. Predictors of mortality in adult patients with ventilator-associated pneumonia: A meta-analysis. Shock. 2010;**33**:590

[10] Davis JS, McMillan M, Swaminathan A, et al. A 16-year prospective study of community-onset bacteriemic Acinetobacter pneumonia: Low mortality with appropriate initial empirical antibiotic protocols. Chest. 2014;**146**:1038

[11] Marchaim D, Chopra T, Bhargava A, et al. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: The role of antimicrobial stewardship. Infection Control and Hospital Epidemiology. 2012;**33**:817

[12] Neidell MJ, Cohen B, Furuya Y, et al. Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. Clinical Infectious Diseases. 2012;**55**:807

[13] Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric therapy for sepsis. Antimicrobial Agents and Chemotherapy. 2010;**55**:807

[14] Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Annals of Internal Medicine. 2001;**134**:298

[15] Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-adquired infection. The New England Journal of Medicine. 2013;**368**:533

[16] Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. Lancet. 2005;**365**:579-587

[17] Pechère JC. Rotating antibiotics in the intensive care unit: Feasible, apparently beneficial, but questions remain. Critical Care. 2002;**6**:9

[18] European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. In: Annual Report of the European Antimicrobial Resistance Network (EARS-Net). Stockholm: ECDC; 2017

# Neonatal Intensive Care

# Current Neonatal Applications of Point-of-Care Ultrasound

Jae H. Kim, Nikolai Shalygin and Azif Safarulla

Additional information is available at the end of the chapter

**Abstract**

Point-of-care ultrasound (POCUS) is an imaging modality that continues to gain acceptance in pediatric and neonatal medicine. In neonatology throughout many areas of the world, functional echocardiography performed by neonatologists has been at the forefront in the growth of POCUS compared to non-cardiac POCUS, the latter which potentially carries more opportunities for use. Despite the early adoption in obstetrics and maternal-fetal medicine, the actual bedside implementation in neonatology has unfortunately been much slower. Examples in neonatology where POCUS may continue to expand include central line placement, endotracheal tube localization, diagnosis of pneumothoraces, cardiac function assessment, and bowel viability assessment just to name a few. This chapter will be a practical synopsis of the most active uses and opportunities for POCUS in neonatology. Expanded training for neonatologists and trainees is required before widespread adoption occurs.

**Keywords:** ultrasound, point of care, newborn, preterm, central catheter, pneumothorax, necrotizing enterocolitis

## 1. Introduction

Point-of-care ultrasound (POCUS) is an imaging modality that continues to gain acceptance in pediatric and neonatal medicine. While ultrasound initially served as a clinical tool with a consultative model with radiology and cardiology disciplines, the value of POCUS in assessment of the heart and other organs is slowly being recognized. In neonatology throughout many areas of the world, functional echocardiography performed by neonatologists has been at the forefront in the growth of POCUS compared to non-cardiac POCUS. Technological

advances have pushed ultrasound (US) to have improved image quality and mobility while reducing cost and size of devices increasing the availability of ultrasound as a point-of-care bedside tool in several areas such as emergency medicine, obstetrics, and intensive care. Despite the early adoption in obstetrics and maternal-fetal medicine, the actual bedside implementation in neonatology has unfortunately been much slower. Examples in neonatology where POCUS may continue to expand include central line placement, endotracheal tube localization, diagnosis of pneumothoraces, cardiac function assessment, and bowel viability assessment just to name a few. What follows is a practical synopsis of the most active uses and opportunities for POCUS in neonatology.

## 2. Head

The newborn brain is readily accessible for sonographic imaging by the open soft tissue windows of the anterior fontanelle and the open sutures found between the unfused cranial bones. Neonatologists are quite familiar with viewing and interpreting cranial ultrasound images as these are routinely reviewed daily on clinical rounds. The primary views are coronal (front to back), sagittal (left to right) and axial views for posterior fossa [1]. POCUS can provide excellent views of the general architecture of the brain especially the two ventricles, evaluation of hemorrhage or calcifications and early evidence of ischemic changes. The use of POCUS for brain imaging is particularly useful when suspect hemorrhage may be responsible for deterioration or hemodynamic instability, at times when sonographic support is not readily available. The detection of increased pressure, cerebral edema or stroke is not sensitive with HUS and other imaging modalities such as CT or MRI are recommended. It is important to remember that these evaluations are limited in evaluating this triangulated view of the brain and can miss events or lesions outside of this window in the parietal regions. Head ultrasound is one of the easier techniques to learn for neonatologists since the views are already very familiar to them. The imaging techniques hinge upon establishing stable upright views of the two hemispheres and axial views of the posterior fossa structures. Neonatal providers have ample experience in reviewing and interpreting head ultrasounds for common pathology such as periventricular leukomalacia, intraventricular and intracranial hemorrhages and so most of the skills are focused on imaging.

## 3. Central catheters

Central vascular catheters such as umbilical arterial catheters (UAC), umbilical venous catheters (UVC), and peripherally inserted central catheters (PICC) are the most common central catheters placed in the sick neonate. Any neonate born at less than 32 weeks gestation will have at least a UVC and/or a PICC during their admission for nutrition and/or medications. In most units all of these lines are placed blind and confirmed with a single radiograph. UVC tip localization by standard radiography is imprecise. In one study approximately 30% of the radiographs were read as normal but actually had the UVC tip in the right atrium when checked with US [2]. Radiographic localization of UVC on anterior–posterior (AP) is difficult

to place in ideal position because of the doming of the diaphragm. The lateral chest radiograph is better than the AP view of the chest but this view is not as convenient with the infant typically secured down for the procedure.

Ultrasound more accurately confirms the position of the catheter tip than radiographs and reduces the exposure of ionizing radiation. Ultrasound guidance results in faster placement and fewer manipulations and radiographs for both umbilical catheters and PICC as compared with conventional placement [3, 4]. POCUS can be very useful in localizing the tip of central catheters either during placement or after a catheter has been placed to follow any migration. Umbilical catheters can frequently migrate after placement in the first few days after insertion. This may be due to drying and shrinkage of a longer umbilical cord. POCUS allows for the direct visualization of the umbilical and PICC catheters and their tips and indirect visualization of the UVC in the hepatic portion of the catheter pathway where it is localized by the shadow cast by the catheter [4]. Ultrasound may be able to help guide the catheter and thereby reduce complications during UVC, UAC, or PICC insertion. Doppler ultrasound is also useful to examine the aorta and renal vessels when placing or evaluating a UAC (**Figure 1**).

Use of POCUS for vascular access for PICCs has been limited due to the greater skillset required to accessing these small veins compared to older children. Setting up dedicated PICC teams can help develop this expertise to promote this aspect of central catheter POCUS.

With US, the UVC can be placed just beyond the IVC-RA junction. This permits good visualization and eliminates any risk of extravasation of the catheter in the liver. The UAC is readily placed just behind the heart which approximates the T7–8 position. The recognition of PICC movement in the large vessels makes it particularly challenging to manage the best position to place these catheters. Movement of the arm or leg to identify the deepest position of the PICC will ensure that the catheter does not inadvertently migrate deeper after placement and cause more risk of complications. For upper PICCs the arm position in a 45 degree flexed position at the shoulder and elbow usually represents the deepest point for a PICC while the knees bent close to the chest represent the deepest point for lower PICCs. The upper PICC can be placed at least 1 cm before the SVC-RA junction while the lower PICC is placed at 1–2 cm below the IVC-RA junction (**Figure 2**).
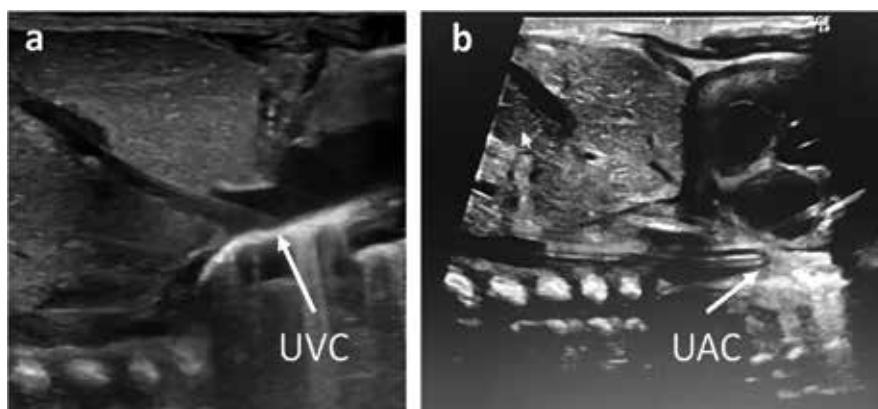


**Figure 1.** Umbilical catheter placement (a) UVC-umbilical venous catheter, (b) UAC-umbilical arterial catheter.
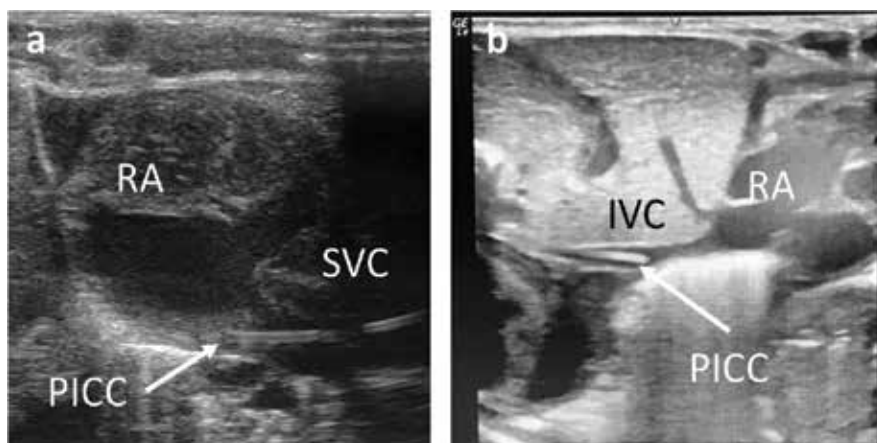
**Figure 2.** PICC localization (a) upper PICC, (b) lower PICC, PICC-peripherally, inserted central catheter, RA-right atrium, SVC-superior vena cava, IVC-inferior vena cava.

Other areas of benefit from POCUS in the NICU are arterial line placement where localization of the vessel and flow identification by Doppler ultrasound can be performed. A modified Allen test with Doppler ultrasound evaluation of collateral flow is useful prior to the procedure. Real-time ultrasound can result in fewer attempts and less chance of a hematoma as compared with palpation.

## 4. Cardiac

The use of echocardiography has aided the evaluation of cardiac anatomy and function of the unborn fetus and the newborn. Ordering an assessment of the heart by ultrasound is a routine practice in the NICU. There has been a need to supplement the clinical assessment and current hemodynamic monitoring as they do not provide a comprehensive picture of cardiac output and organ perfusion states. The need for serial measurements is another unmet need with routine cardiac echocardiograms since transitional physiology after birth and during illness often require repeated measurements. Bedside POCUS for cardiac assessment is still an emerging practice as training to evaluate the heart is one of the hardest POCUS skills. Despite its difficulty there are probably more neonatologists worldwide with training to assess the heart through limited functional assessments than there are for non-cardiac POCUS. Cardiac POCUS is not intended to replace a cardiology assessment or structural echocardiogram. It is intended to be limited and dynamic assessment of hemodynamic of the heart to help with clinical decision making. Cardiac assessment in neonates is unique due to the dynamic changes that occur in the first few weeks of life making it challenging to order frequent dynamic assessments. The ability to help determine rapid determination of hemodynamics with serial functional assessments makes it increasingly attractive to work it into the daily workflow [5]. The focus of neonatal cardiac POCUS is to concentrate on a limited set of assessments that are helpful in determining the real-time hemodynamics. These include assessment of the patent ductus arteriosus (PDA), ventricular function, filling of the heart and volume assessment.
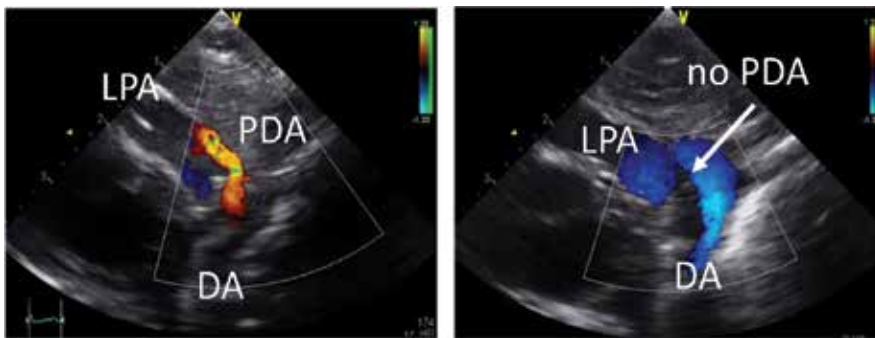
**Figure 3.** PDA (a) large PDA, (b) no PDA, LPA-left pulmonary artery, DA-descending aorta.

To start, cardiac POCUS can provide a rapid qualitative assessment of contractility: normal, hyperactive, reduced contractility (mild, moderate, or severe). Fractional shortening measurements are relatively easy to obtain and provide quantitative information. Cardiac filling as a measure of volume assessment can also be determined quickly. The PDA represents an important shunt to assess to facilitate clinical management to determine if the PDA is contributing to cardiorespiratory compromise or systemic hypoperfusion. The PDA can be determined to be open or closed (**Figure 3**). The presence of a patent ductus arteriosus can lead to an overestimate of cardiac output using usual left ventricular output measurements. An alternative measure of cardiac output using superior vena caval flow (SVC) measurements as a surrogate measure has been proposed [6–9]. Unfortunately, SVC flow has not become widely used as it has proven to be difficult to minimize inter-operator variability in this measurement. While several examples of benefit of neonatal cardiac POCUS have been published, there remains a paucity of neonatal clinical studies to validate each of the functional assessments and their ability to improve diagnostic or management of the sick neonate [10, 11]. As more neonatologists become comfortable with the skillset of cardiac echocardiography, there is a need for improved standardization and quality assurance [12, 13]. There have been some attempt to standardize the practice but many feel that the standards set are excessive and restrict early adoption [14, 15]. The anatomic assessment of the heart for the most part should be left to the cardiologist but it is equally important to recognize patterns of normal structure to know when there is suspicion of a congenital heart lesion.

Nevertheless, despite a number of hurdles, there remains tremendous promise that neonatal cardiac POCUS can provide a focused assessment to provide hemodynamic information to the bedside clinician.

# 5. Lung

The evaluation of lung by POCUS in neonates is increasingly practiced as the imaging technique is relatively simple and the lung is readily accessible for interrogation through the chest wall. Several recent articles have noted lung ultrasound to be as good if not better than X-ray as a diagnostic modality. Reduction in cost of image acquisition and exposure to ionizing

radiation improves quality of care as well as patient safety [16]. Neonatal lung POCUS is similar to pediatric lung POCUS except that the neonate has very thin soft tissue in the chest with thin ribs and a cartilaginous sternum that enables larger windows of viewing. From a technical perspective, we need a high frequency transducer like a 7–15 MHz hockey stick or equivalent linear array transducer. The detection of common respiratory conditions has been documented making it potentially possible to define the parenchymal lung disease by characteristic patterns to the common respiratory conditions such as pneumonia (PNA), transient tachypnea of the newborn (TTN) and respiratory distress syndrome (RDS). The ability to make an urgent diagnosis is where the greatest utility of lung POCUS may lie as acute respiratory compromise often requires rapid diagnostics. The presence of air or fluid such as blood, transudate or exudate in the pleural space is readily discernable by US.

The complication of spontaneous pneumothorax (PTX) at birth is one such condition that may be aided by lung POCUS. PTX will display several differing US patterns compared to normal lung. The characteristic findings on US of PTX in neonates are similar to adults and children (**Figure 4**). Normal lung appears homogeneous in texture with the occasional presence of hyperechoic linear A (horizontal) and B (vertical) lines. Movement of the parietal and visceral pleura against each other during respiration creates a "shimmering effect" or an "ants marching effect" which is termed lung sliding. The presence of the sliding lung sign rules out a pneumothorax on B mode [17]. Further confirmation of a PTX can be achieved with M mode which displays the data from a single line in an image mapped against time on the x-axis. The appearance of moving lung tissue results in a granular appearance similar to a sandy "seashore" with the "waves" at the top representing the static soft tissue above the lungs. Some data suggests that US may not be as sensitive for PTX in neonates [18].

The underlying changes in RDS involve loss of the smallest airspaces (alveoli or saccules). This generates denser tissue that gives the appearance of "white lung" using lung POCUS. Some have proposed a scoring system to categorize lung disease in RDS to assist in increasing specificity for diagnosing RDS [19]. This score can reliably predict the need for surfactant treatment in preterm babies less than 34 weeks gestation treated with nasal CPAP from birth. Several
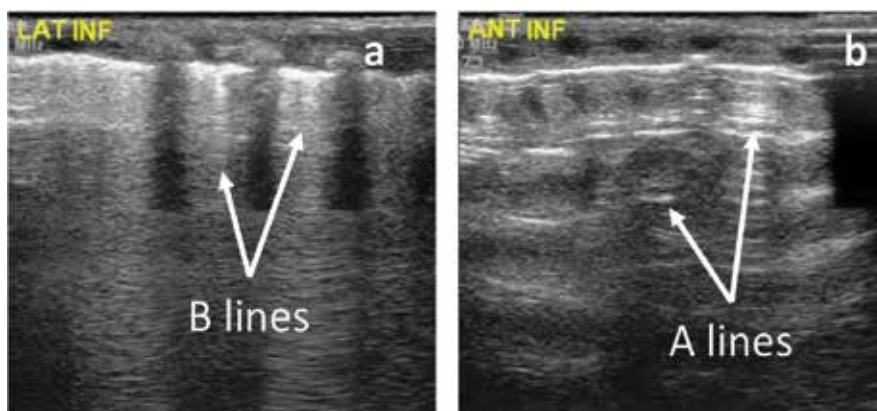


**Figure 4.** Pneumothorax (a) normal lung, (b) pneumothorax.

studies have validated the ability to distinguish between RDS and transient tachypnea of the newborn (TTN) [20, 21]. In TTN ultrasound changes include abnormalities of pleural lines, absence of A-lines, and interstitial syndrome or pulmonary edema. Pneumonia has been described to have A-lines, interstitial syndrome and possible lung consolidation. Lung POCUS has been able to differentiate meconium aspiration syndrome from other respiratory conditions since it is also associated with absent A-lines, lung consolidation, and interstitial syndrome.

The role of lung ultrasound may not replace chest radiographs but may offer more time sensitive information and reduce the total number of radiographs taken. The evaluation of lung by POCUS in neonates is increasingly being studied and practiced. The most promising application may be during resuscitation where early detection and management of conditions like pneumothoraces and pleural effusions are life-saving.

## 6. Endotracheal tube

Neonatal intubation remains a difficult high level skill. Although there are much less intubations taking place compared to a decade ago, the need to establish a secure airway remains ever important. This is particularly true for resuscitation of neonates <28 weeks gestation. The current standard of practice to confirm the placement of the endotracheal tube (ETT) is with chest x-ray (CXR).The passage of the ETT into the trachea or esophagus can be discerned readily using a transverse probe position in adults and pediatric subjects [22–25]. POCUS can be used to rapidly and accurately visualize the anatomic position of the ETT position in preterm and term infants [26] (**Figure 5**). Unlike in pediatric or adult patients, evaluating the ETT in the newborn
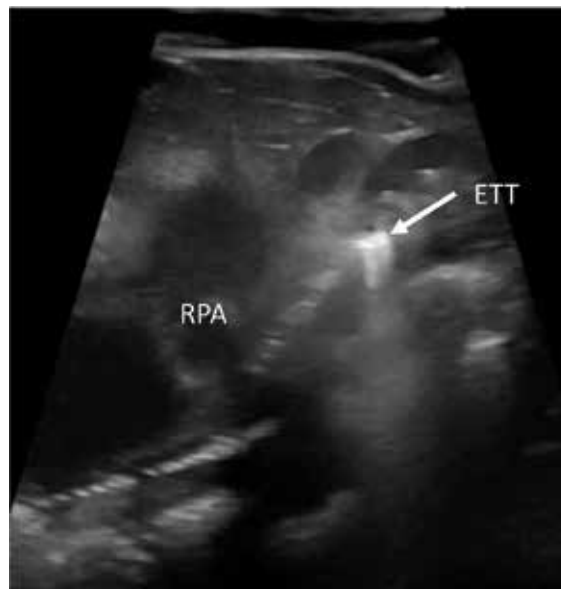


**Figure 5.** Endotracheal tube placement ETT-endotracheal tube, RPA-right pulmonary artery.

through the chest is possible due to the cartilaginous sternum. Although there is air inside and around the ETT and the entry is at a steep angle to the ultrasound probe, the tip of the probe can be identified with a white or hyperechoic line. The ideal location for the tip of the ETT is midway between the thoracic inlet and the carina. Identifying the distance of the tip of the ETT from the carina can be accurately measured. In a recent publication of an extensive database literature search on studies relating to US use for ETT position confirmation found nine studies which collectively reported a > 80% visualization of the ETT tip by US [22]. Also, US interpretation of the ETT position correlated with the XR position in 73–100% of cases. US appears comparable to XR determining ETT position in this population. As US is more easily available and is safer than CXR, it may be a better modality for confirming proper placement of ETT in neonates when time is critical. There are no current data yet on identifying tip location during placement of the ETT and so more clinical data may be required before widespread adoption.

## 7. Bowel

The assessment of bowel by POCUS in neonates remains an emerging practice despite the availability of clinical data in neonates for more than a decade. POCUS can show dynamic intestinal peristalsis as well as characterize the physical nature and perfusion of bowel that can be used to assess bowel integrity and viability. The newborn can be affected by a variety of congenital and acquired bowel conditions that may lead to significant bowel dysfunction or even death. Early recognition of the signs of impending bowel injury or the progression of bowel damage is essential. Intestinal peristalsis can be quantified by counting cumulative motility events over time to give an objective assessment of bowel movement [27]. Identifying peristalsis can assist in the routine management of neonatal feeding or bowel assessment but more studies are required to validate its utility for clinical outcomes (**Figure 6**). Some other studies have demonstrated that gastroesophageal reflux can be evaluated by POCUS both identifying anatomic risk factors as well as visualizing the bolus but this has not gained traction in clinical practice yet [28, 29].

Recent data suggest that dedicated abdominal ultrasound examination may be of utility in the diagnosis and management of infants with necrotizing enterocolitis (NEC). Advantages of ultrasound include assessment of peristalsis, vascular perfusion, bowel-wall thickening, and abdominal fluid. Absence of ionizing radiation is an added benefit. A recent meta-analysis showed that bowel ultrasound is increasingly being recognized as an important imaging tool for evaluating NEC that provides additional detail over plain abdominal radiographs [30]. There are still only few studies with small case series and heterogeneous gestational age population that have investigated the comparison between plain radiographs and abdominal ultrasound in predicting the outcomes of patients with NEC.

NEC is one of the most severe gastrointestinal conditions affecting neonates. The risk increases with degree of prematurity and in those with low birth weight [31–35]. Although risk factors have been identified, the etiology is still not well recognized. Despite significant advances in neonatal care, mortality in NEC remains high (between 20 and 60% in a group of most immature neonates) and maintained at the same level. Therefore, in cases of clinically suspected

**Figure 6.** Normal bowel appearance.

NEC quick diagnostics and implementation of appropriate treatment are crucial [34–36]. Diagnosis is based on clinical presentation, laboratory testing and imaging. Traditionally, the gold standard for imaging evaluation of the neonatal intestine is the intestinal gas pattern on plain abdominal radiographs; however interpretation can be challenging with intestinal gas pattern being nonspecific [37–39], and significant overlap between radiographic signs of NEC and other intestinal pathology [40].

The usefulness of abdominal ultrasound in the diagnosis of NEC has been known since 1984 as evidenced in a number of studies [41–43]. Studies have looked at ultrasound being an adjunct to diagnose and manage infants with NEC. It allows for an earlier detection of typical signs of NEC, with more rapid disease management. When compared with abdominal radiographs in predicting NEC, studies showed that they can depict bowel distension, to some extent bowel-wall thickness, pneumatosis intestinalis, portal venous air and free abdominal air which ultrasound could easily depict as well. More importantly, abdominal ultrasound provides important additional information regarding viability of bowel wall viability and free fluid, which might aid in diagnosis and management of NEC [44, 45]. With color Doppler specific suspicious loops of bowel can be interrogated to reveal if they are perfused or not which enables the identification of non-viable bowel with a high degree of certainty. The gradual progression of NEC can be identified by POCUS from the initial hyperemia and swelling of bowel wall to the dilatation with increased disease and then thinning of bowel wall with loss of perfusion or blood flow. Therefore, nonviable bowel will no longer have any blood flow present (**Figure 7 Epelman diagram)**. The detection of portal venous gas is much easier by POCUS than by radiographs [46].

### 7.1. Procedure and features

For performing bowel ultrasound a linear probe of 8–15 MHz probe (higher frequency for higher resolution and lower depth targeting superficial structures). Features that are key include: (a) bowel wall thickening >2.6 mm, (b) increase in bowel wall echogenicity, (c) portal venous air, (d) pneumatosis Intestinalis and free air and (e) intra-abdominal fluid.
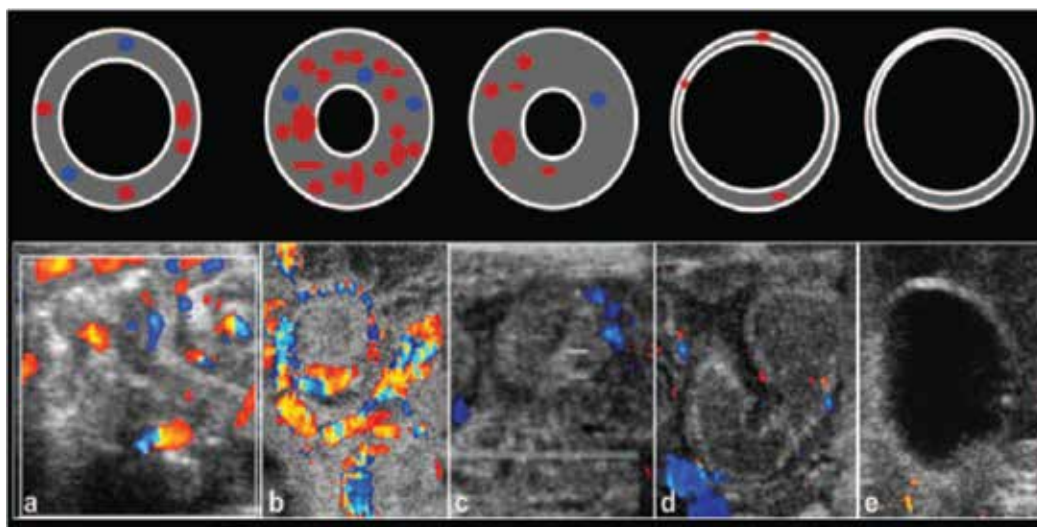
**Figure 7.** Sonographic appearance of NEC progression (figure from Epelman et al. 38 need permission).

Some limitations of ultrasound include that it is operator or skill dependent and this is a real time diagnosis which might create an obstacle for radiologists to evaluate the ultrasounds retrospectively and in turn underlines the need for neonatologists to be more familiar with this tool. Currently most of the available literature are single center trials, retrospective observational cohorts. We still need more prospective studies doing head to head trials with abdominal radiograph to understand the true value and usefulness of abdominal US. More studies are required to fully validate these assessments in clinical care. Training of radiologist and their sonographers as well as other providers such as neonatologists and surgeons is required before broad adoption of bowel POCUS occurs.

## 8. Bladder

Bladder aspiration through suprapubic urine collection is ideal to perform under ultrasound guidance over landmark techniques. Ultrasound of the bladder can help determine the size and location of the bladder and the volume of urine in the bladder. Portable ultrasound can significantly improve the diagnostic yield; a minimum volume on ultrasound of 10 mL is associated with a 90% successful bladder aspiration. If the cephalocaudal diameter of the bladder (sagittal view) is >20 mm and the anteroposterior diameter is >15 mm, the success rate approaches 100%.

## 9. Lumbar puncture

Lumbar puncture (LP) is a relatively common procedure performed in emergency department and the NICU as part of a complete sepsis evaluation. The LP is typically performed using the "blind" surface landmark guidance. Anecdotally, this technique is reported to be have a high percentage of success. However successful identification of landmarks has been

shown to be accurate only 30% of the time [47]. Traumatic or unsuccessful LPs in this group have been documented in the pediatric literature in 30–50% of patients [48, 49]. This translates to increased difficulty in obtaining CSF and higher rate of complications such as local/subdural/epidural hematoma, bloody tap and incomplete sepsis evaluation to name a few. Fluoroscopy guided LP is an alternative but challenges include limited availability, radiation exposure, need to transport critical patients for the procedure.

Use of POCUS for identification of key landmarks is a safe and easy alternative to the blind method [50–52]. In adults, using ultrasound for LP has been associated with a reduction in the number of attempts and interspaces accessed [51–55]. In neonates, the incompletely ossified spinous processes, minimal fat aids in interrogation of the space by ultrasound compared to older kids and adults. The good resolution of image, lack of ionizing radiation and potential for real time guidance makes ultrasound a valuable tool for performing LP in neonates [48, 56].

LP can be performed in the neonate without general anesthesia or sedation, using oral sucrose and local anesthesia. Patient can be in lateral decubitus position or sitting up. Using ultrasound to measure the interspinous space at L3-L4 and L4-L5 in varying positions, the lumbar spine is found to be maximally positioned in both neonates and children in the seated position with flexed hips versus the lateral decubitus position [57, 58]. The probe used is the 7–15 MHz hockey stick or equivalent linear array transducer. There is still very limited knowledge on ultrasound guided LP in neonates. There are two techniques described in literature, the transverse approach and longitudinal approach based on how the probe is held.

The first skill is to define the landmarks for the LP procedure. Using a surgical marker or pen one can delineate the location of midline and the position of the conus, the point where the spinal cord ends. There are no studies validating the guidance of the needle into the interspace and so this will require more studies before guidance by US is a routine procedure.

## 10. Summary

Existing and emerging POCUS applications are numerous and promising but more validation for clinical value is required in addition to larger scale training of individuals to learn and become competent in these techniques. Emphasis should be on training all incoming and existing fellows to learn POCUS.

## Author details

Jae H. Kim[1]*, Nikolai Shalygin[1] and Azif Safarulla[2]

*Address all correspondence to: neojae@ucsd.edu

1 University of California San Diego and Rady Children's Hospital of San Diego, San Diego, California, USA

2 Augusta University, Augusta, Georgia, USA

# References

[1] Bhat V, Bhat V. Neonatal neurosonography: A pictorial essay. Indian Journal of Radiology Imaging. 2014;**24**(4):389-400

[2] Karber BC et al. Optimal radiologic position of an umbilical venous catheter tip as determined by echocardiography in very low birth weight newborns. Journal of Neonatal-Perinatal Medicine. 2017;**10**(1):55-61

[3] Katheria AC, Fleming SE, Kim JH. A randomized controlled trial of ultrasound-guided peripherally inserted central catheters compared with standard radiograph in neonates. Journal of Perinatology. 2013;**33**(10):791-794

[4] Fleming SE, Kim JH. Ultrasound-guided umbilical catheter insertion in neonates. Journal of Perinatology. 2011;**31**(5):344-349

[5] Poon WB, Wong KY. Neonatologist-performed point-of-care functional echocardiography in the neonatal intensive care unit. Singapore Medical Journal. 2017;**58**(5):230-233

[6] Evans N. Diagnosis of the preterm patent ductus arteriosus: Clinical signs, biomarkers, or ultrasound? Seminars in Perinatology. 2012;**36**(2):114-122

[7] Kluckow M, Seri I, Evans N. Echocardiography and the neonatologist. Pediatric Cardiology. 2008;**29**(6):1043-1047

[8] Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2000;**82**(3):F188-F194

[9] Kluckow M, Evans N. Superior vena cava flow in newborn infants: A novel marker of systemic blood flow. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2000;**82**(3):F182-F187

[10] Sehgal A, Paul E, Menahem S. Functional echocardiography in staging for ductal disease severity: Role in predicting outcomes. European Journal of Pediatrics. 2013;**172**(2):179-184

[11] Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus? European Journal of Pediatrics. 2009;**168**(8):907-914

[12] Finan E et al. Targeted neonatal echocardiography services: Need for standardized training and quality assurance. Journal of Ultrasound in Medicine. 2014;**33**(10):1833-1841

[13] Lee HC, Silverman N, Hintz SR. Diagnosis of patent ductus arteriosus by a neonatologist with a compact, portable ultrasound machine. Journal of Perinatology. 2007;**27**(5):291-296

[14] Mertens L et al. Targeted neonatal echocardiography in the neonatal intensive care unit: Practice guidelines and recommendations for training: Writing group of the American Society of Echocardiography (ASE) in collaboration with the European Association

of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). European Journal of Echocardiography. 2011;**12**(10):715-736

[15] Singh Y et al. Expert consensus statement 'Neonatologist-performed echocardiography (NoPE)'-training and accreditation in UK. European Journal of Pediatrics. 2016;**175**(2):281-287

[16] Hall EJ. Lessons we have learned from our children: Cancer risks from diagnostic radiology. Pediatric Radiology. 2002;**32**(10):700-706

[17] Kurepa D, Zaghloul N, Watkins L, Liu J. Neonatal lung ultrasound exam guidelines. Journal of Perinatology. 2018 Jan;**38**(1):11-22

[18] Liu DM et al. Utilization of ultrasound for the detection of pneumothorax in the neonatal special-care nursery. Pediatric Radiology. 2003;**33**(12):880-883

[19] Brat R et al. Lung ultrasonography score to evaluate oxygenation and surfactant need in neonates treated with continuous positive airway pressure. JAMA Pediatrics. 2015;**169**(8):e151797

[20] Liu J et al. Lung ultrasonography to diagnose transient tachypnea of the newborn. Chest. 2016;**149**(5):1269-1275

[21] Sawires HK et al. Use of lung ultrasound in detection of complications of respiratory distress syndrome. Ultrasound in Medicine & Biology. 2015;**41**(9):2319-2325

[22] Jaeel P, Sheth M, Nguyen J. Ultrasonography for endotracheal tube position in infants and children. European Journal of Pediatrics. 2017;**176**(3):293-300

[23] Slovis TL, Poland RL. Endotracheal tubes in neonates: Sonographic positioning. Radiology. 1986;**160**(1):262-263

[24] Sethi A et al. Point of care ultrasonography for position of tip of endotracheal tube in neonates. Indian Pediatrics. 2014;**51**(2):119-121

[25] Tejesh CA et al. Sonographic detection of tracheal or esophageal intubation: A cadaver study. Saudi Journal of Anaesthesia. 2016;**10**(3):314-316

[26] Dennington D et al. Ultrasound confirmation of endotracheal tube position in neonates. Neonatology. 2012;**102**(3):185-189

[27] Richburg DA, Kim JH. Real-time bowel ultrasound to characterize intestinal motility in the preterm neonate. Journal of Perinatology. 2013;**33**(8):605-608

[28] Pezzati M et al. Diagnosis of gastro-oesophageal reflux in preterm infants: Sonography vs. pH-monitoring. Neonatology. 2007;**91**(3):162-166

[29] Koumanidou C et al. Sonographic measurement of the abdominal esophagus length in infancy: A diagnostic tool for gastroesophageal reflux. AJR. American Journal of Roentgenology. 2004;**183**(3):801-807

[30] Cuna AC et al. Bowel ultrasound for predicting surgical management of necrotizing entero-colitis: A systematic review and meta-analysis. Pediatric Radiology. 2017;**48**(5):658-666

[31] Schnabl KL et al. Necrotizing enterocolitis: A multifactorial disease with no cure. World Journal of Gastroenterology. 2008;**14**(14):2142-2161

[32] Neu J, Walker WA. Necrotizing enterocolitis. The New England Journal of Medicine. 2011;**364**(3):255-264

[33] Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet. 2006;**368**(9543):1271-1283

[34] Holman RC et al. Necrotising enterocolitis hospitalisations among neonates in the United States. Paediatric and Perinatal Epidemiology. 2006;**20**(6):498-506

[35] Clark RH et al. Characteristics of patients who die of necrotizing enterocolitis. Journal of Perinatology. 2012;**32**(3):199-204

[36] Luig M et al. Epidemiology of necrotizing enterocolitis–part II: Risks and susceptibility of premature infants during the surfactant era: A regional study. Journal of Paediatrics and Child Health. 2005;**41**(4):174-179

[37] Rehan VK et al. Observer variability in interpretation of abdominal radiographs of infants with suspected necrotizing enterocolitis. Clinical Pediatrics (Phila). 1999;**38**(11):637-643

[38] Baird R et al. Imaging, radiation exposure, and attributable cancer risk for neonates with necrotizing enterocolitis. Journal of Pediatric Surgery. 2013;**48**(5):1000-1005

[39] Coursey CA et al. Radiologists' agreement when using a 10-point scale to report abdominal radiographic findings of necrotizing enterocolitis in neonates and infants. American Journal of Roentgenology. 2008;**191**(1):190-197

[40] Epelman M et al. Necrotizing enterocolitis: Review of state-of-the-art imaging findings with pathologic correlation. Radiographics. 2007;**27**(2):285-305

[41] Yikilmaz A et al. Prospective evaluation of the impact of sonography on the management and surgical intervention of neonates with necrotizing enterocolitis. Pediatric Surgery International. 2014;**30**(12):1231-1240

[42] Raboisson MJ et al. Assessment of uterine artery and aortic isthmus Doppler recordings as predictors of necrotizing enterocolitis. American Journal of Obstetrics and Gynecology. 2012;**206**(3): 232 e1-6

[43] Akin MA et al. Quantitative assessment of hepatic blood flow in the diagnosis and management of necrotizing enterocolitis. The Journal of Maternal-Fetal & Neonatal Medicine. 2015;**28**(18):2160-2165

[44] Higashizono K et al. Postoperative pneumatosis intestinalis (PI) and portal venous gas (PVG) may indicate bowel necrosis: A 52-case study. BMC Surgery. 2016;**16**(1):42

[45] Nevins EJ et al. A rare case of ischaemic pneumatosis intestinalis and hepatic portal venous gas in an elderly patient with good outcome following conservative management. International Journal of Surgery Case Reports. 2016;**25**:167-170

[46] Bohnhorst B et al. Early feeding after necrotizing enterocolitis in preterm infants. The Journal of Pediatrics. 2003;**143**(4):484-487

[47] Furness G, Reilly MP, Kuchi S. An evaluation of ultrasound imaging for identification of lumbar intervertebral level. Anaesthesia. 2002;**57**(3):277-280

[48] Coley BD, Shiels WE 2nd, Hogan MJ. Diagnostic and interventional ultrasonography in neonatal and infant lumbar puncture. Pediatric Radiology. 2001;**31**(6):399-402

[49] Glatstein MM et al. Incidence of traumatic lumbar puncture: Experience of a large, tertiary care pediatric hospital. Clinical Pediatrics (Phila). 2011;**50**(11):1005-1009

[50] Dietrich AM, Coley BD. Bedside pediatric emergency evaluation through ultrasonography. Pediatric Radiology. 2008;**38**(Suppl 4):S679-S684

[51] Ozdamar E et al. Ultrasound-assisted lumbar puncture in pediatric emergency department. Pediatric Emergency Care. 2017;**33**(8):e21-e23

[52] Nomura JT et al. A randomized controlled trial of ultrasound-assisted lumbar puncture. Journal of Ultrasound in Medicine. 2007;**26**(10):1341-1348

[53] Brousseau AA, Parent MC. Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 3: Advantages of ultrasound-assisted lumbar puncture. Emergency Medicine Journal. 2016;**33**(2):163-165

[54] Strony R. Ultrasound-assisted lumbar puncture in obese patients. Critical Care Clinics. 2010;**26**(4):661-664

[55] Shaikh F et al. Ultrasound imaging for lumbar punctures and epidural catheterisations: Systematic review and meta-analysis. BMJ. 2013;**346**:f1720

[56] Abukawa Y et al. Ultrasound versus anatomical landmarks for caudal epidural anesthesia in pediatric patients. BMC Anesthesiology. 2015;**15**:102

[57] Abo A et al. Positioning for lumbar puncture in children evaluated by bedside ultrasound. Pediatrics. 2010;**125**(5):e1149-e1153

[58] Oncel S et al. Positioning of infants in the neonatal intensive care unit for lumbar puncture as determined by bedside ultrasonography. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2013;**98**(2):F133-F135

# Neurological Critical Care

# Important Issues in Coma and Neuromonitoring

Bogdan Pavel

Additional information is available at the end of the chapter

**Abstract**

Coma is defined as a state of unconsciousness and lack of response to noxious stimuli. The physiopathology of consciousness and coma is not entirely understood. On the other hand, clinical examination does not give us enough information in all types of coma states. In this chapter, some types of coma and their definition, the necessity of coma monitoring and what we can use for coma monitoring in ICU, algorithms for EEG monitoring, BIS, AppEntropy, permutation entropy and auditory evoked potentials are described. Burst suppression state new theories and cortical connectivity and reactivity during coma as a tool for coma prognosis will be on focus.

**Keywords:** coma status, burst suppression, cortical connectivity, cortical reactivity

## 1. Introduction

Coma is defined as a state of loss of consciousness and lack of response to external stimuli that occurs in pathological states and during anesthesia. The prognosis of coma patients is difficult to assess, as the mechanism through which coma occurs is not entirely understood. What we may do is evaluate cerebral function, through accurate and careful monitoring. Thus, the intensive care specialist requires one or several instruments to monitor the cerebral function of coma patients, as it is difficult to perform, even hourly, a clinical evaluation, taking into account the typical workload of the doctor.

In certain circumstances, a worsening neurological state does not manifest itself clinically—an example being nonconvulsive status, which has negative prognostic value in the case of traumatic brain injury (TBI), and can only be diagnosed through continuous electroencephalographic monitoring (EEG).

**Figure 1.** Continuous BIS (bispectral index) and NIRS (near-infrared spectroscopy) monitoring during anesthesia.

Continuous EEG monitoring and cerebral oximetry monitoring—through the NIRS (near-infrared spectroscopy) technique—are useful instruments that provide the doctor with real-time, vital information on the coma patient. These techniques have the advantage of noninvasivity, ease of use and they can provide the doctor with easily quantifiable scores. Perhaps most importantly, they can be made available continuously at the bedside (**Figure 1**).

Unfortunately, there is not one single standard monitor at this moment to accurately estimate what occurs in the brain of a coma patient. Therefore, in this chapter, we shall start with a brief exposition on coma physiopathology, insisting on burst suppression (BS) state, and we shall continue with the characteristics of the main coma states we might encounter in the intensive care unit (ICU). We will continue with the devices used to monitor anesthesia depth, which are used to monitor coma depth as well. These devices are based on EEG signal analysis. The main drawback of EEG signal analysis is noise: how shall we define and remove noise on an EEG?

A definitive answer is difficult to find, that is why "noise-resistant" mathematical algorithms have been developed. Thus, this chapter focuses on the mathematical algorithms used to interpret EEG signal, as it is important to know the basis of parameters and scores we receive from the devices we use. In the end, we describe new theories that might be standardized to evaluate coma state—such as cortical connectivity and reactivity.

## 2. Coma state

### 2.1. Coma—definition and theories

Coma is defined as a state of unconsciousness and lack of response to noxious stimuli. The physiopathology of consciousness and coma state is not entirely understood. It is not clear if a "coma center" exists or if the diverse pathological states that induce coma do so through different mechanisms. From this perspective, coma is similar to the anesthetic state, which is caused by several pharmacological agents, with different chemical structures. It is also unclear if a common center, on which all anesthetics act, exists. Based on histology and physiology, Sir Francis Crick postulated that the claustrum has a central role in maintaining consciousness (as it is connected with nearly all cerebral structures), like the conductor of an orchestra [1]. Recent studies have shown that during isoflurane anesthesia on the rat,

functional connectivity of the claustrum with medial prefrontal cortex and mediodorsal thalamus decreased [2]. As for coma state, there are no definitive studies proving the role of the claustrum in its physiopathology.

Regarding EEG activity, comas are different. The same coma state, defined by a lack of consciousness and of response to external pain stimuli may exhibit different EEG aspects. Thus, there are comas with prevalent alpha waves (alpha comas), beta waves (beta comas), theta waves (theta comas) or delta waves (delta comas). A common characteristic of these coma states is that if they are secondary to intoxication or metabolic encephalopathies, they have a positive prognosis, regardless of the EEG pattern, with response to external pain stimuli. If there are secondary to brain stem lesions or hypoxic ischemic encephalopathies and lacking response to external pain stimuli, comas bring a negative prognosis [3].

Comas secondary to TBI are caused by diffuse axonal injury (DAI) and by hemorrhages that compress the brain stem. Diffuse axonal injury occurs due to rapid (rotational) acceleration, which causes lacerations in the neuronal cytoskeleton and therefore block neuronal transport [4]. Hameroff and Penrose support the hypothesis that conscious processes are based in the microtubules of the neuronal cytoskeleton [5, 6]. Furthermore, it is known that volatile anesthetics interfere with the function of these microtubules. Nevertheless, if this theory proves true—that consciousness is based on and influenced by neuronal cytoskeleton microtubules—that might explain loss of consciousness secondary to diffuse axon injury.

Another etiology of coma is nonconvulsive status, defined as prolonged seizures there are not clinically manifested and associate altered mental status [7], secondary to TBI (8–16%), to stroke—HAS (3–31%) and craniotomy [8]. The mechanism of loss of consciousness during epilepsy is not entirely understood. Blumenfeld Hal et al. affirm that a common mechanism exists—a cortico-subcortical network dysfunction. Therefore, a decrease in cerebral blood flow (CBF) was noticed in frontoparietal association areas and the anterior and posterior interhemispheric regions with (CBF) increases in bilateral midline subcortical structures [9].

Besides, a loss of connectivity between medial and lateral frontoparietal association areas and upper brainstem/medial diencephalon was observed [10]. They state that these cortico-subcortical connectivity malfunctions (occurring in generalized tonic-clonic seizures, complex partial seizures and temporal lobe seizures) are caused either by indirect inhibition or by convulsions initiated in these structures.

### 2.2. Burst suppression (BS) state

Burst suppression is a cortical electrical activity defined by the existence of high-amplitude and variable frequency waves discharge, followed by a period of electrical activity suppression. BS is an intermediate state between slow waves EEG pattern and an isoelectric line. This BS pattern is present in several conditions, such as Ohtahara syndrome, TBI, hypoglycemia, hypoxia, hypothermia and anesthesia [11]. As for anesthesia bursts, they have a wave morphology specific to each anesthetic compound, and a different duration as well. In addition, the length of the burst decreases as the anesthesia depth increases [12]. Not only is the burst length variable, but so is its structure, according to its length. Thus, we have noticed [13] that for isoflurane anesthesia in rat, 4-seconds bursts and 1-second bursts have different aspects
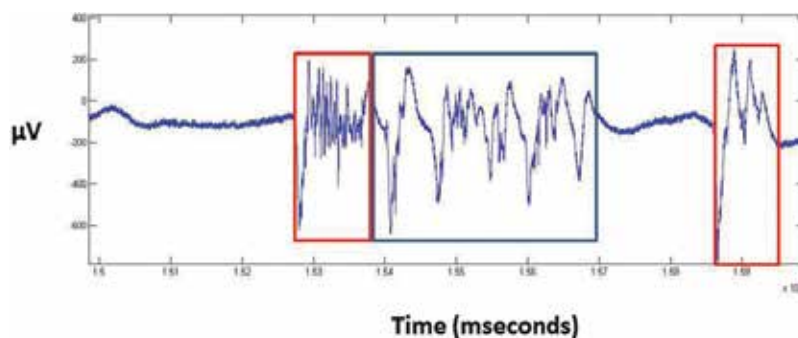
**Figure 2.** Burst aspects according to its length (local-field potential—LFP—recording). The first burst lasts almost 4 seconds and presents high-frequency waves at the beginning followed by slow waves. The second burst is short (almost 1 second) and presents slow waves.

(**Figure 2**). Long bursts start with high-frequency high-amplitude waves, followed by low-frequency high-amplitude waves, while short bursts present low-frequency high-amplitude waves as it is seen on power spectral density graphics (**Figure 3**).

Even though a BS presenting coma state is considered deep, BS is deemed a state of hyper-excitability, as bursts can be evoked by subliminal stimuli [14] and BS electrical activity is correlated with cerebral blood flow changes as well [15].

The mechanism supporting this phenomenon remains incompletely explained. We have two theories attempting an explanation at the moment. The metabolic theory of Emery Brown [11]
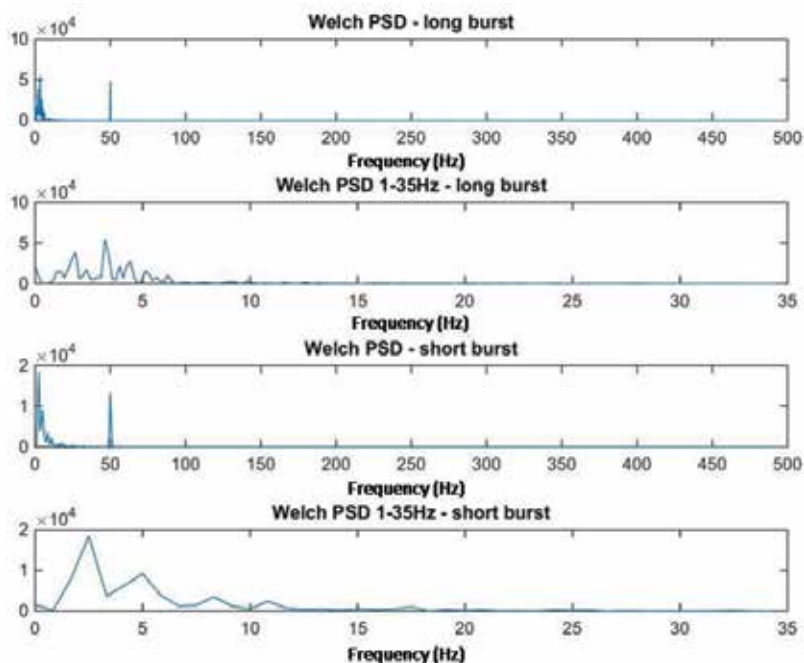


**Figure 3.** Power spectral density during the long burst versus the short burst. Two peaks of frequencies can be observed in the long burst.

is based on the fact that BS states correlate with low metabolism states (with low metabolic rate), such as hypothermia, anesthesia and hypoglycemia. The link between the electrical and the metabolic activity is the KATP channels, so during the burst, ATP concentration decreased which induces an increase in the conductance of KATP and thus a neuronal membrane hyper-polarization occurs (flat-line EEG). The theory of Amzica [16] states that BS activity is modulated by extracellular calcium concentration variations, thus the depletion of the extracellular cortical calcium during the burst is responsible for the EEG silence (flat line) after that. The basis of this phenomenon is unclear as well. It is regarded that bursts are caused by internal input, modulated by neural networks. On the other hand, the cortex has been proven to exhibit BS activity, without the intervention of subcortical structures [17].

In the clinical practice, finding BS patterns in coma patients presents a negative prognostic value, if the BS ratio (BSR = suppression time/epoch duration * 100) is over 20–23% [18].

## 3. EEG monitoring and interpretation

### 3.1. Continuous EEG monitoring

Continuous EEG monitoring is the most used and, perhaps, the most efficient method of evaluating coma patients in the ICU. The advantage is the electrode placing: it is noninvasive (or minimally invasive), can be easily applied on the scalp of the patient and requires a minimal qualification of the ICU staff. Most EEG recording devices include software for mathematically processing the signal, and generating scores or frequencies.

The acquisition system 10–20, that is classically used, provides an overview of the main cortical areas. Placing the electrodes and fastening them with a specialized helmet may facilitate CT or MRI transportation, in order to obtain a complex imagistic and electroencephalographic representation. Standard EEG monitoring provides information on the onset of epileptic seizures, is useful in detecting nonconvulsive status and in detecting early and late ischemia, secondary to subarachnoid hemorrhage. Furthermore, it provides useful information (based on prevailing EEG patterns and reactivity) for the prognostic of the coma patient [19].

The following chapter will describe the main mathematical algorithms that are used in analyzing EEG signal, as well as the devices used for monitoring coma and anesthesia depth.

### 3.2. EEG signal analysis

#### 3.2.1. Spectral analysis

Spectral analysis of EEG signal is based on the fast Fourier transformation (FFT), which decomposes the signal according to the mean amplitude of each frequency in the signal. By applying second-order FFT, the result is the spectral power graphic, which decomposes the signal based on amplitude squared/frequency (microvolts$^2$/Hz). Analyzing this graphic provides very important parameters to estimate the depth of sedation/anesthesia.

Median frequency (MEF) represents the value of frequency whose perpendicular meets Ox in the point that splits equally the area under the spectral power graphic.

Spectral edge frequency (SEF) is the value of frequency from which we can draw a perpendicular to Ox that leaves 90 or 95% of the spectral power function under graphic area to the left [20] (**Figure 4**).

If the patient is anesthetized, the values of these parameters will decrease proportionally with the degree of sedation (they will shift to the left), because during sedation, the high-frequency fast waves EEG activity ceases [21]. Surgical anesthesia is performed at the moment the EEG shows mostly theta waves.

*3.2.2. EEG signal entropy*

Entropy represents the degree of disorder in a system. Ludwig Boltzmann defines entropy as the logarithmic function of the number of microstates corresponding to a macrostate. In 1949, Claude Shanon defines information entropy as being:

$$S = \sum_{i=1}^{n} P(x) \log P(x) \tag{1}$$

where S = entropy,

P = apparition probability,

log = binary logarithm.

As EEG is a signal composed of several types of waves, with a disorderly aspect, the more disorderly (more types of waves), the higher the entropy. An isoelectric EEG signal has a null entropy. This type of entropy, applied to EEG signals, was used to monitor anesthetic depth during desflurane anesthesia [22]. The Datex-Ohmeda company (now acquired by GE) developed a device that analyzes EEG signal entropy and displays it as a score.
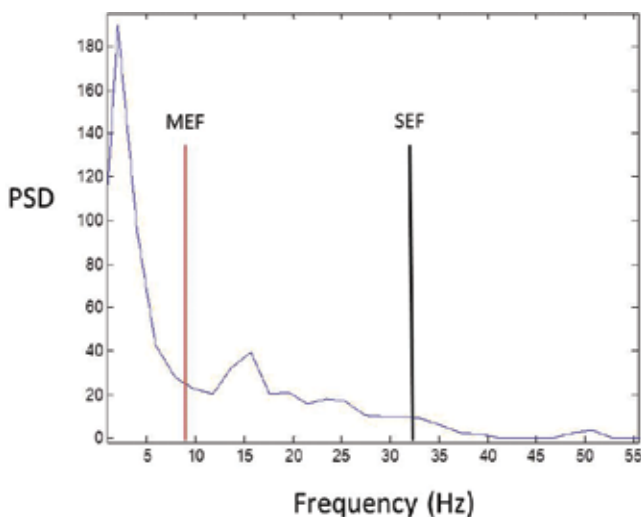


**Figure 4.** EEG power spectrum density (PSD). In this figure, median frequency (MEF) and spectral edge frequency (SEF) are displayed on the PSD graph.

The EEG signal entropy calculation is based on the following algorithm:

$$SN[f1, f2] = \frac{S[f1, f2]}{\log(N[f1, f2])}$$   (2)

where [f1, f2] = frequencies between which the EEG signal is analyzed,

N[f1, f2] = number of frequencies between f1 and f2.

The EEG signal is acquired at a frequency of 400 Hz, and to analyze it, several epochs (windows) are used, between 0.92 and 60.16 seconds, in order to cover all EEG signal frequencies. The shortest epoch is used to analyze frequencies between 32 and 47 Hz, and the 60.16 epoch to analyze frequencies under 2 Hz. The device provides two entropy indices: state entropy (SE) and response entropy (RE). SE analyzes EEG in the frequency domain 0.8–32 Hz, while RE in the 0.8–47 Hz frequency domain. The difference between RE and SE is given by the EMG activity: it is assumed that an increase of entropy in the 32–47 Hz domain corresponds to an increase of frontal electromyographic activity, and this difference shows indirectly the quality of intraoperative analgesia). SE is between 0 and 91, and RE is between 0 and 100.

During anesthesia, the values displayed by the entropy monitor must be in the range of 40–60 in order to prevent waking up during the intervention [23–25].

### 3.2.3. Bispectral index

The Aspect Medical company was the first to market a monitor for anesthesia depth, in 1994 [26]. It is based on the bispectral analysis of EEG signal [27]. The monitor analyzes the EEG recorded by prefrontal electrodes, based on an algorithm, undisclosed entirely up until today [28]. This algorithm calculates a score between 0 (isoelectric line) and 100 (patient awake). This algorithm was validated by correlating the clinical sedation score, lack of response to pain stimulation and EEG parameters for approximately 1500 patients (cumulating approximately 5000 hours of recordings). BIS monitoring evaluates well the degree of sedation/hypnosis of anesthesia, and not directly the anesthetic depth. It was validated for all volatile and intravenous anesthetic, except ketamine. As this generates thalamocortical dissociation, the EEG is similar to that of an awake patient. During sevoflurane anesthesia, ketamine may increase the BIS score, though anesthesia deepens [29]. In the case of propofol anesthesia, analgesic dose of ketamine does not influence the bispectral index [30–32]. Though xenon has a similar mechanism to ketamine and was not used in the validation process of the BIS monitor, it modifies the EEG similarly to propofol [33]. As for correlating the BIS score, older studies have stated that BIS under 50 does not ensure hypnosis [34]. A more recent study reveals that xenon anesthesia depth clinical signs correlate well with BIS score values [35].

The algorithm used incorporates spectral analysis, bispectral analysis and burst-suppression activity analysis (BS). Spectral analysis, described above, decomposes the signal based on the amplitude of each frequency, analyzing data individually and ignoring the relationship with other constituents. In the human brain, there are several EEG signal generators. While the patient is awake, the EEG signal is produced by the independently emitted activity of several generators, only slightly synchronized. As the patient falls asleep or is anesthetized,

the number of active generators decreases and they become more synchronized. Bispectral analysis quantifies the phase-phase coupling between these EEG signal generators.

BIS components are *beta ratio* and *SyncFastSlow*. Beta ratio is the logarithm of the ratio of two frequency components of the spectral power (30–47 Hz and 11–20 Hz), while *SyncFastSlow* is the logarithm of the bispectral ratio of 0.5–47 Hz and 40–47 Hz [36].

$$BetaRatio \ = \ \log\left(\frac{P\,30-47}{P\,11-20}\right) \tag{3}$$

$$SyncFastFlow \ = \ \log\left(\frac{B\,0.5-47}{B\,40-47}\right) \tag{4}$$

BIS monitors display several parameters, such as the BIS score value (between 0 and 100), which should be maintained during anesthesia between 40 and 60 to prevent waking up, signal quality index, suppression ratio for a 60 seconds epoch (SR), the minute burst count (BC), frontal electromyographic activity (EMG)—which results from analyzing the EEG signal in the 70–110 Hz frequency interval (assumed to be produced by spontaneous frontal muscles activity) and is between 30 and 55 dB [37].

BIS monitoring can be used in the intensive care wards as well, to monitor patient sedation [38]: in traumatic brain injury, a value under 60 correlates with a negative prognosis [39]. BIS monitoring may also be used to detect cerebral vasospasm in critical patients [40]; it has been proven that it correlates well with the consciousness level of the ICU patients, it aids in adjusting sedative dosage, it has a prognostic value and it is useful in monitoring induced coma for a status epilepticus [41–44].

EMG activity is not greatly influenced by the degree of curare neuromotor block, but the pain stimulus EMG variation during anesthesia depends on the degree of neuromuscular block [45].

### 3.2.3.1. BIS monitoring limitations

BIS analysis of EEG signal provides information only on the sedation during anesthesia, and not on global anesthetic depth. The BIS score does not accurately predict when the patient will regain consciousness. Recent studies have shown that both loss of consciousness and waking up from anesthesia correlate with gamma cortical activity, as losing consciousness is caused by gamma rhythm cessation [46, 47]. BIS monitors cannot gather gamma rhythm EEG signal, as it can only be optimally recorded through dura mater electrodes.

BIS monitors pick up EEG signal in the prefrontal area, where spontaneous electromyographic activity interferes with gamma rhythm frequency. The BIS score cannot predict pain stimuli hemodynamic reactivity during anesthesia and is influenced by the type of anesthetic used—volatile anesthesia, for the same anesthetic potency, differently alter EEG activity. Furthermore, it is not influenced by cerebral perfusion and hypoglycemia [48].

### 3.2.4. Narcotrend monitoring

This monitor was marketed in 2000 by the Monitor Technik company. The EEG signal is picked up by three electrodes in the frontal area. It is then filtered and noise is removed. EEG is analyzed in the 0.5–47 Hz frequency domain. The algorithm includes the relative power of alpha, beta, theta and delta frequencies, median frequency, spectral edge frequency and spectral entropy. This monitor displays values between 0 and 100. The depth of anesthesia is divided into five stages [49]. The values provided by this monitor are well correlated with the ones provided by BIS monitoring [50]. The Narcotrend monitor has been proven useful in the post-operative care of the patients who underwent propofol sedation during cardiac surgery [51].

### 3.2.5. Consciousness index

The monitor for the consciousness index is a wireless, portable monitor as well, with a 10-meters range. It is produced by Morpheus Medical. It provides a score with values between 0 and 100, and, similar to the BIS monitoring during anesthesia, the value of the consciousness index must be maintained between 40 and 60 to prevent waking up during anesthesia. This monitor analyzes EEG, using symbolic dynamic analysis. As EEG is a variation of potential through time, it can be seen as a dynamic system, in which every moment has a state that can be defined through a real number. The dynamic symbol method analyzes a dynamic system as being composed of a discrete sequence of abstract symbols that each correspond to a system state [52].

This monitor was compared with BIS monitoring and similar results were found [53].

There is one other consciousness index that uses Lempel-Ziv complexity analysis. This method was established in 2013 by a team of researchers led by Adenauer Casali and Olivia Gosseries. This index was studied during midazolam sedation and propofol-xenon anesthesia, on a limited number of subjects. It is based on evaluating cortical reactivity and intercortical connectivity, using high-density EEG and transcranial magnetic stimulation on several cortical areas: superior occipital gyrus, superior medial frontal gyrus, superior parietal gyrus and premotor rostral cortex. EEG signals were analyzed using the Lempel-Ziv complexity algorithm, which approximates the amount of nonredundant information in a binary system, thus estimating the minimal amount of patterns required to describe a signal. The less EEG signal nonredundant information there is, the less complex the signal and deep the anesthesia is [54].

### 3.2.6. Approximate entropy

Entropy is the degree of disorder in a system, thus an extensive measurement of chaos. At the beginning of the twentieth century, the mathematicians Andrey Kolmogorov and Henri Poincare further developed the mathematical analysis of chaos. In 1991, Steven Pincus introduced the notion of approximate entropy. Approximate entropy measures the complexity of a system. As it is little influenced by noise, it has an advantage in the analysis of systems exposed to a strong source of noise. Mathematically, approximate entropy quantifies how constant the distance between two vectors in a series is [55].

The following formula is used to calculate approximate entropy:

$$ApEn(Sn, m, r) \; = \; \ln\left(\frac{C_m(r)}{C_{m+1}(r)}\right) \tag{5}$$

where m = length of the pattern,

Cm(r) = prevalence of repetitive patterns, with the length m.

Applied to time series, approximate entropy is a measurement of series predictability. As we know, electroencephalographic signal is a time variation of scalp-recorded potential. Thus, electroencephalographic signal may be described as a time series. Calculating approximate entropy, there results an estimation of EEG signal predictability, and, inherently, an estimation of the signal complexity. The more awake the patient is, the higher values the approximate entropy will have, as the EEG is more complex and less predictable. During deep sedation, EEG complexity lowers and thus will be more predictable, with a lower approximate entropy value.

Approximate value is used to estimate anesthesia depth and correlates well with BIS and SEF indices, during propofol-remifentanil anesthesia [56].

### 3.2.7. Permutation entropy

Permutation entropy is another method of estimating the chaos, which analyzes the probability of appearance of a motive of amplitude over a certain amount of time. The more motifs there are, the more complex the signal is, therefore the more awake the patient is. When the probability of appearance of all motifs is equal, permutation entropy equals 1. The calculation algorithm for the permutation entropy was published in 2002 by Bandt, and in 2008, Jordan et al. use this algorithm to study electroencephalograms [57, 58].

$$PE \; = \; -\frac{\sum P_i \times \ln P_i}{\ln N} \tag{6}$$

where P = probability of appearance of a motif,

N = number of motifs.

An important parameter is the signal acquisition frequency, the algorithm being designed for a frequency of 100 or 128 Hz.

In 2008, Olofsen et al. studied EEG by using permutation entropy during propofol anesthesia and described six types of motifs: peaks, slopes and grooves [59].

Using permutation entropy, the transition between loss of consciousness and consciousness can be detected by analyzing 2-seconds EEG recordings [60].

### 3.2.8. EEG fractality

Fractal analysis of the EEG signal implies measuring the degree of self-similarity of the signal. EEG fractal analysis was used to study sleep, anesthesia or convulsions [61–63].

Another analysis parameter for complexity, similar with fractal analysis, is detrended fluctuation analysis (DFA). It is an analysis method for signal self-similarity and was used to evaluate EEG and was suggested as a possible quantification parameter of anesthesia depth [64].

*3.2.9. Auditory evoked potentials*

Changes in the latency and amplitude of auditory evoked potentials of middle latency (early cortical), that appear 20–80 ms after auditory stimulation, can be correlated with anesthetic depth [65–67].

The auditory evoked potential index (AAI) is an algorithm integrating amplitude variations of several consecutive potentials and generating a numerical outcome, between 0 and 99, similar to the bispectral index [68]. Patients lose consciousness under 40, and surgical anesthesia appears under 20. AAI values are well correlated with BIS values [69]. In the ICU, middle latency evoked potentials have a positive prognostic value in the patients who required craniotomy for TBI, and there has been noticed a strong correlation between pupillary responses, intracranial pressure and auditory evoked potentials in patients with supratentorial mass lesions [70, 71].

# 4. Near-infrared spectroscopy (NIRS)

Jobsis first noticed in 1977 [72] that tissues are transparent for a wavelength of light of 700–950 nm. Based on this, the concentration of oxyhemoglobin, deoxyhemoglobin and cytochrome C oxidase can be measured (only the first two are used in clinical practice).

Starting from the oxyHb and deoxyHb concentrations, one can estimate regional saturation of oxygen ($rSO_2$) in a tissue. Furthermore, the regional changes of blood flow can be assessed, by evaluating the changes of total hemoglobin (HbT). Monitors for cerebral oxygenation, that are based on the NIRS technology, use a sensor placed above the tissue, whose oxygenation is to be measured. The sensor is made of emitting and detecting diodes, placed within 4–8 cm of each other. Detecting diodes will detect the infrared light reflected by the tissue. In the case of cerebral tissue, the infrared light can penetrate up to a depth of 0.6–1 centimeters [73]. Thus, cerebral oxygenation through this method is underestimated, compared with jugular vein saturation ($SjVO_2$) [74]. Among the benefits of this method are the noninvasive character and the ease of use at the bedside.

In the case of the brain, $rSO_2$ values are closer to the venous saturation than to arterial saturation because 70% of cerebral blood is in the veins and capillaries, and thus, normal cerebral $rSO_2$ values are between 60 and 80%. Using NIRS in the current clinical practice began in the 1980s, with the first studies on monitoring cerebral function in the adult and neonate. More recent studies are focused upon evaluating prehospital coma gravity. For example, Peters et al. [75] observed in a study including 25 patients that NIRS has a sensitivity of 93.3% and a specificity of 78.6% over CT scans in detecting intracranial hematoma.

Additionally, NIRS values have prognostic value in TBI patients. The values of $rSO_2$ at hospital admission were 74.7 ± 1.5% in the case of surviving patients and 61.9 ± 19.4%

in nonsurvivors [76]; therefore, $rSO_2$ under 60% are associated with increased mortality. In the case of resuscitated SCR patients, $rSO_2$ in the first 24 hours was 68.2% for survivors and 62.9% for nonsurvivors [77]. As for blood flow variation monitoring, it was noticed that the cerebral oximetry index (Cox), determined through NIRS, is a good substitute of the mean velocity index (Mx)—determined through transcranial Doppler echography (TCD) [78]. NIRS is also useful in detecting vasospasm in subarachnoid hemorrhage (SAH) patients as well [79].

## 5. Cortical connectivity and coma

During coma states as during the anesthesia, there is a decrease in connectivity ("communication") between different cortical regions, or between cortical and subcortical regions, caused by a reduction of cerebral activity. The basis of cortical connectivity is made of structural links, such as synapses and neural fibers.

In clinical practice, the evaluation of connectivity is performed by analyzing the coherence/correlation between biological signals (EEG, ECoG and local-field potentials) from different regions of the brain.

*Functional connectivity* is based on biological signals analysis, which can be described as time series (such as the EEG) and can quantify cortical connectivity using statistical analysis (correlation) of the EEG signals from different cortical areas. The better the EEG signals are correlated (estimated by the correlation coefficient, XAppEn, mscohere), the more they are alike; therefore, there is a good connectivity between the cortical areas. Importantly, good statistical correlation of biological signals does not necessarily involve causality, and does not point out the direction the information moves [80]. Unlike structural connectivity, functional connectivity is time-dependent [81].

*Effective connectivity* may be regarded as a unit of structural and functional connectivity. It is the latest instrument trying to establish causal relations between neural network components [81]. Effective connectivity is calculated using complex mathematical algorithms (such as Granger causality or transfer entropy), applied to time series.

The state of consciousness, according to Buzsaki (2007), is the consequence of the functional transformation of information contained by a neural network. Both posterior parietal and prefrontal association areas and frontoparietal network information integration were considered involved in the generation and maintenance of the state of consciousness [82, 83]. During sleep, which is a reversible modification of consciousness as well, there is a modification of cortical connectivity; therefore, during NREM sleep, it lowers and during REM sleep, it increases [84].

Cortical connectivity changes during anesthesia were first observed in lab animals, and then in humans. Thus, in 2005, the cortical connectivity changes, especially in the prefrontal cortex, during sevoflurane anesthesia of different concentrations, were described. Bouveroux et al. described the effects of propofol on cortical connectivity: during propofol anesthesia, corticocortical and thalamocortical connectivity decreases in frontal-parietal networks, while it is

maintained in the visual and auditory cortex [85]. Mhuircheartaigh et al. regard the lack of response to auditory and pain stimuli during propofol anesthesia as a consequence of putamen-cortex connectivity decreases, while thalamocortical connectivity remains unchanged [86]. Ferrarelli et al. notice as well the frontal intracortical connectivity decreases, during transcranial magnetic stimulation, under midazolam sedation [87]. Cortical connectivity is disrupted in several pathological states, such as brain trauma, vegetative state and memory or attention loss.

During mild brain trauma, there have been described frontal and occipital cortical connectivity changes, a decrease of intercortical connectivity over longer distances and an increase of cortical connectivity over shorter distances [88]. The vegetative state is defined as the abolishing of consciousness, while excitatory external factors are present. While in vegetative state, there is a decrease of cortical connectivity in several areas: prefrontal and premotor cortex, temporal-parietal association areas and posterior cingulate cortex. Furthermore, there is an altered connectivity between prefrontal and premotor cortical areas and posterior cingulate cortex [89]. Subcortical cerebrovascular accidents alter cortical connectivity between the two hemispheres: between supplementary motor areas and between ipsilateral supplementary motor area and lateral premotor area. These neural connectivity modifications, both under physiological and under pathological conditions, make cortical connectivity, if not the most sensitive, among the most sensitive parameters of nervous function.

### 5.1. Evaluating cortical connectivity

*5.1.1. Mathematical algorithms to estimate cortical connectivity*

*Functional cortical connectivity* may be estimated by calculating the correlation coefficient between signals of different regions, the covariance or the coherence of two or several signals. The disadvantage of these algorithms is the inability to determine the direction of data exchange between cortical and subcortical areas.

*Effective cortical connectivity* is estimated with the direct transfer function (DTF), based on Granger causality. Named after Clive Granger, econometrician awarded the Nobel Memorial Prize in Economic Sciences in 2003, the Granger linear systems causality states that for two time series (such as two EEG channels) with a unidirectional data exchange from the Y series to the X series, the modifications from the Y series will be found after a certain amount of time in the X series, or that analyzing Y series data can better predict X series modifications. By evaluating effective connectivity through DTF, we may analyze several time series/ EEG channels. This algorithm was developed by Polish mathematicians Kaminski and Blinowska in 1991 [90].

BSMART is a cortical connectivity analysis software package that can run on the MATLAB program.

Cortical connectivity can also be evaluated through imagistic methods (such as MRI) or electrophysiological methods (EEG).

High-density electroencephalography (64–256 electrodes) can provide information on intercortical connectivity, and is based on EEG signal analysis of different cortical regions. It has the advantage of being usable bedside, and data analysis can be performed more quickly than in the case of imagistic methods [91, 92].

## 6. Cortical reactivity and coma state

Evaluating cortical reactivity in coma patients seems to be a useful prognostic tool. In 1995, Gütling noticed that cortical reactivity to external stimuli at 48 and 72 hours correlates well with the neurological outcome at 1.5 years after the incident, in the case of severe head injury [93]. More recent studies, performed by Logi and Rossetti, have shown that the presence of EEG reactivity in coma caused by a traumatic brain injury, a cerebrovascular disease or post-anoxic coma after a cardiac arrest associates a good outcome [94, 95]. Although these studies on using cortical reactivity in the evaluation of coma patients prognostic were published in the 1990s, there is no standardization in this matter, neither of evoked potential type, nor of reactivity-evaluating algorithm one should use.

Particularly useful is the BS state, usually correlated with a negative prognostic. Although regarded as a deep coma state, applying visual, auditory **or** somatosensory stimuli under the BS state gives rise to evoked bursts under isoflurane anesthesia, as proven by Hartikainen [96]. During burst suppression states, cortical reactivity seems to rise proportionally with the suppression, with maximal cortical reactivity at a BS ratio of 40–80%. Additional studies are required to validate a parameter for the cortical reactivity of coma patients.

## Author details

Bogdan Pavel[1,2]*

*Address all correspondence to: pavelbogdan2009@gmail.com

1 Division of Physiology and Neurosciences, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

2 Emergency Hospital Plastic Surgery and Burns, Bucharest, Romania

## References

[1] Crick FC, Koch C. What is the function of the claustrum? Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2005;**360**(1458):1271-1279

[2] Smith JB, Liang Z, Watson GDR, Alloway KD, Zhang N. Interhemispheric resting-state functional connectivity of the claustrum in the awake and anesthetized states. Brain Structure & Function. 2017;**222**(5):2041-2058

[3] Sutter R, Kaplan PW. Electroencephalographic patterns in coma: When things slow down. Epileptologie. 2012;**29**:201-209

[4] Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. Experimental Neurology. 2013;**246**:35-43

[5]  Hameroff S, Penrose R. Consciousness in the universe: A review of the 'Orch OR' theory. Physics of Life Reviews. 2014;**11**(1):39-78

[6]  Penrose R. Shadows of the Mind: An Approach to the Missing Science of Consciousness. Oxford: Oxford University Press; 1994

[7]  Chang AK, Shinnar S. Nonconvulsive status epilepticus. Emergency Medicine Clinics of North America. 2011;**29**(1):65-72

[8]  Kubota Y, Nakamoto H, Kawamata T. Nonconvulsive status epilepticus in the neurosurgical setting. Neurologia Medico-Chirurgica (Tokyo). 2016;**56**(10):626-631

[9]  Yu L, Blumenfeld H. Theories of impaired consciousness in epilepsy. Annals of the New York Academy of Sciences. 2009;**1157**:48-60

[10]  Blumenfeld H. Impaired consciousness in epilepsy. Lancet Neurology. 2012;**11**(9):814-826

[11]  Ching S, Purdon PL, Vijayan S, Kopell NJ, Brown EN. A neurophysiological-metabolic model for burst suppression. Proceedings of the National Academy of Sciences of the United States of America. 2012;**109**(8):3095-3100

[12]  Akrawi WP, Drummond JC, Kalkman CJ, Patel PM. A comparison of the electrophysiologic characteristics of EEG burst-suppression as produced by isoflurane, thiopental, etomidate, and propofol. Journal of Neurosurgical Anesthesiology. 1996;**8**(1):40-46

[13]  Pavel B, Acatrinei CA, Menardy F, Zahiu CMD, Popa D, Zagrean AM, Zagrean L. Changes of cortical connectivity during deep anaesthesia. Romanian Journal of Anaesthesia and Intensive Care. 2015;**22**(2):83-88

[14]  Kroeger D, Amzica F. Hypersensitivity of the anesthesia-induced comatose brain. The Journal of Neuroscience. 2007;**27**(39):10597-10607

[15]  Liu X, Zhu XH, Zhang Y, Chen W. Neural origin of spontaneous hemodynamic fluctuations in rats under burst-suppression anesthesia condition. Cerebral Cortex. 2011;**21**(2):374-384

[16]  Amzica F. Basic physiology of burst-suppression. Epilepsia. 2009;**50**(Suppl 12):38-39

[17]  Topolnik L, Steriade M, Timofeev I. Partial cortical deafferentation promotes development of paroxysmal activity. Cerebral Cortex. 2003;**13**(8):883-893

[18]  Theilen HJ, Ragaller M, Tschö U, May SA, Schackert G, Albrecht MD. Electroencephalogram silence ratio for early outcome prognosis in severe head trauma. Critical Care Medicine. 2000;**28**(10):3522-3529

[19]  Caricato A, Melchionda I, Antonelli M. Continuous electroencephalography monitoring in adults in the intensive care unit. Critical Care. 2018;**22**(1):75

[20]  Tonner PH, Bein B. Classic electroencephalographic parameters: Median frequency, spectral edge frequency etc. Best Practice & Research. Clinical Anaesthesiology. 2006;**20**(1):147-159

[21]    Martín-Cancho MF, Lima JR, Luis L, Crisóstomo V, López MA, Ezquerra LJ, Carrasco-Jiménez MS, Usón-Gargallo J. Bispectral index, spectral edge frequency 95% and median frequency recorded at varying desflurane concentrations in pigs. Research in Veterinary Science. 2006;**81**(3):373-381

[22]    Bruhn J, Lehmann LE, Röpcke H, Bouillon TW, Hoeft A. Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. Anesthesiology. 2001;**95**(1):30-35

[23]    Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Meriläinen P. Description of the entropy algorithm as applied in the Datex-Ohmeda S/5 entropy module. Acta Anaesthesiologica Scandinavica. 2004;**48**(2):154-161

[24]    Vakkuri A, Yli-Hankala A, Sandin R, Mustola S, Høymork S, Nyblom S, Talja P, Sampson T, van Gils M, Viertiö-Oja H. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. Anesthesiology. 2005;**103**(2):274-279

[25]    Vakkuri A, Yli-Hankala A, Talja P, Mustola S, Tolvanen-Laakso H, Sampson T, Viertiö-Oja H. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiologica Scandinavica. 2004;**48**(2):145-153

[26]    Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. Journal of Clinical Monitoring. 1994;**10**(6):392-404

[27]    Abarbanel H, Davis R, MacDonald GJ, Munk W. Bispectra. Defense Technical Information Center, Document ADA150870; 1984

[28]    Bruhn J, Bouillon TW, Shafer SL. Bispectral index (BIS) and burst suppression: Revealing a part of the BIS algorithm. Journal of Clinical Monitoring and Computing. 2000;**16**(8):593-596

[29]    Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on bispectral index and spectral entropy of the electroencephalogram under sevofluraneanaesthesia. British Journal of Anaesthesia. 2005;**94**(3):336-340

[30]    Faraoni D, Salengros JC, Engelman E, Ickx B, Barvais L. Ketamine has no effect on bispectral index during stable propofol-remifentanilanaesthesia. British Journal of Anaesthesia. 2009;**102**(3):336-339

[31]    Sengupta S, Ghosh S, Rudra A, Kumar P, Maitra G, Das T. Effect of ketamine on bispectral index during propofol–fentanyl anesthesia: A randomized controlled study. Middle East Journal of Anesthesiology. 2011;**21**(3):391-395

[32]    Nonaka A, Makino K, Suzuki S, Ikemoto K, Furuya A, Tamaki F, Asano N. Low doses of ketamine have no effect on bispectral index during stable propofol-remifentanil anesthesia. Masui. 2012;**61**(4):364-367

[33] Laitio RM, Kaskinoro K, Särkelä MO, Kaisti KK, Salmi E, Maksimow A, Långsjö JW, Aantaa R, Kangas K, Jääskeläinen S, Scheinin H. Bispectral index, entropy, and quantitative electroencephalogram during single-agent xenon anesthesia. Anesthesiology. 2008;**108**(1):63-70

[34] Goto T, Nakata Y, Saito H, Ishiguro Y, Niimi Y, Suwa K, Morita S. Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anaesthesia. British Journal of Anaesthesia. 2000;**85**(3):359-363

[35] Fahlenkamp AV, Krebber F, Rex S, Grottke O, Fries M, Rossaint R, Coburn M. Bispectral index monitoring during balanced xenon or sevoflurane anaesthesia in elderly patients. European Journal of Anaesthesiology. 2010;**27**(10):906-911

[36] Antognini JF, Carstens E, Raines DE. Neural Mechanism of Anesthesia. NJ, USA: Humana Press; 2002

[37] Nunes RR, Chaves IM, de Alencar JC, Franco SB, de Oliveira YG, de Menezes DG. Bispectral index and other processed parameters of electroencephalogram: an update. Rev Bras Anestesiol. Jan-Feb, 2012;**62**(1):105-117

[38] Zhao D, Xu Y, He W, Li T, He Y. A comparison of bispectral index and sedation agitation scale in guiding sedation therapy: A randomized controlled study in patients undergoing short term mechanical ventilation. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2011;**23**(4):220-223

[39] Li HL, Miao WL, Ren HX, Lin HY, Wang HP. The value of bispectral index in the unconscious patients with acute brain injury due to different pathogenic factors. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013;**25**(3):174-176

[40] Brallier JW, Deiner SG. Use of the bilateral BIS monitor as an indicator of cerebral vasospasm in ICU patients. Middle East Journal of Anesthesiology. 2013;**22**(2):161-164. PubMed PMID: 24180164

[41] Mondello E, Siliotti R, Noto G, Cuzzocrea E, Scollo G, Trimarchi G, Venuti FS. Bispectral index in ICU: Correlation with Ramsay score on assessment of sedation level. Journal of Clinical Monitoring and Computing. 2002;**17**(5):271-277

[42] Mahmood S, Parchani A, El-Menyar A, Zarour A, Al-Thani H, Latifi R. Utility of bispectral index in the management of multiple trauma patients. Surgical Neurology International. 2014;**5**:141

[43] Dou L, Gao HM, Lu L, Chang WX. Bispectral index in predicting the prognosis of patients with coma in intensive care unit. World Journal of Emergency Medicine. 2014;**5**(1):53-56.

[44] Musialowicz T, Mervaala E, Kälviäinen R, Uusaro A, Ruokonen E, Parviainen I. Can BIS monitoring be used to assess the depth of propofol anesthesia in the treatment of refractory status epilepticus? Epilepsia. 2010;**51**(8):1580-1586

[45] Ekman A, Stålberg E, Sundman E, Eriksson LI, Brudin L, Sandin R. The effect of neuromuscular block and noxious stimulation on hypnosis monitoring during sevoflurane anesthesia. Anesthesia and Analgesia. 2007;**105**(3):688-695

[46]  John ER, Prichep LS. The anesthetic cascade: A theory of how anesthesia suppresses consciousness. Anesthesiology. 2005;**102**:447-471

[47]  Imas OA, Ropella KM, Ward BD, Wood JD, Hudetz AG. Volatile anesthetics disrupt frontal-posterior recurrent information transfer at gamma frequencies in rat. Neuroscience Letters. 2005;**387**:145-150

[48]  Duarte LT, Saraiva RA. When the bispectral index (bis) can give false results. Revista Brasileira de Anestesiologia. 2009;**59**(1):99-109. Review

[49]  Kreuer S, Wilhelm W. The Narcotrend monitor. Best Practice & Research. Clinical Anaesthesiology. 2006;**20**(1):111-119. Review. PubMed PMID: 16634418

[50]  Schultz A, Siedenberg M, Grouven U, Kneif T, Schultz B. Comparison of narcotrend index, bispectral index, spectral and entropy parameters during induction of propofol-remi-fentanilanaesthesia. Journal of Clinical Monitoring and Computing. 2008;**22**(2):103-111

[51]  Weber F, Steinberger M, Ritzka M, Prasser C, Bein T. Measuring depth of sedation in intensive care patients with the electroencephalographic narcotrend index. European Journal of Anaesthesiology. 2008;**25**(2):123-128

[52]  Musizza B, Ribaric S. Monitoring the depth of anaesthesia. Sensors (Basel). 2010;**10**(12): 10896-10935

[53]  Chakravarthy M, Holla S, Jawali V. Index of consciousness and bispectral index values are interchangeable during normotension and hypotension but not during non pulsatile flow state during cardiac surgical procedures: A prospective study. Journal of Clinical Monitoring and Computing. 2010;**24**(2):83-91

[54]  Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, Casarotto S, Bruno MA, Laureys S, Tononi G, Massimini M. A theoretically based index of consciousness independent of sensory processing and behavior. Science Translational Medicine. 2013;**5**(198):198ra105

[55]  Pincus SM. Approximate entropy as a measure of system complexity. Proceedings of the National Academy of Sciences of the United States of America. 1991;**88**(6):2297-2301

[56]  Bruhn J, Bouillon TW, Radulescu L, Hoeft A, Bertaccini E, Shafer SL. Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of "anesthetic depth" during coadministration of propofol and remifentanil. Anesthesiology. 2003;**98**(3):621-627

[57]  Bandt C, Pompe B. Permutation entropy: A natural complexity measure for time series. Physical Review Letters. 2002;**88**(17):174102

[58]  Jordan D, Stockmanns G, Kochs EF, Pilge S, Schneider G. Electroencephalographic order pattern analysis for the separation of consciousness and unconsciousness: An analysis of approximate entropy, permutation entropy, recurrence rate, and phase coupling of order recurrence plots. Anesthesiology. 2008;**109**(6):1014-1022

[59]  Olofsen E, Sleigh JW, Dahan A. Permutation entropy of the electroencephalogram: A measure of anaesthetic drug effect. British Journal of Anaesthesia. 2008;**101**(6):810-821

[60] Kreuzer M, Kochs EF, Schneider G, Jordan D. Non-stationarity of EEG during wakefulness and anaesthesia: Advantages of EEG permutation entropy monitoring. Journal of Clinical Monitoring and Computing; 2014

[61] Yeh JR, Peng CK, Lo MT, Yeh CH, Chen SC, Wang CY, Lee PL, Kang JH. Investigating the interaction between heart rate variability and sleep EEG using nonlinear algorithms. Journal of Neuroscience Methods. 2013;**219**(2):233-239

[62] Willand M, Rudner R, Olejarczyk E, Wartak M, Marciniak R, Stasiowski M, Byrczek T, Jałowiecki P. Fractal dimension–A new EEG-based method of assessing the depth of anaesthesia. Anestezjologia Intensywna Terapia. 2008;**40**(4):217-222

[63] Wang Y, Zhou W, Yuan Q, Li X, Meng Q, Zhao X, Wang J. Comparison of ictaland interictal EEG signals using fractal features. International Journal of Neural Systems. 2013;**23**(6):1350028

[64] Jospin M, Caminal P, Jensen EW, Litvan H, Vallverdú M, Struys MM, Vereecke HE, Kaplan DT. Detrended fluctuation analysis of EEG as a measure of depth of anesthesia. IEEE Transactions on Biomedical Engineering. 2007;**54**(5):840-846

[65] Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Doré CJ, Newton DE, Jones JG. The auditory evoked response as an indicator of awareness. British Journal of Anaesthesia. 1989;**63**(1):113-115

[66] Schwender D, Kaiser A, Klasing S, Peter K, Pöppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. Anesthesiology. 1994;**80**(3):493-501

[67] Newton DE, Thornton C, Konieczko KM, Jordan C, Webster NR, Luff NP, Frith CD, Doré CJ. Auditory evoked response and awareness: A study in volunteers at sub-MAC concentrations of isoflurane. British Journal of Anaesthesia. 1992;**69**(2):122-129

[68] Mantzaridis H, Kenny GN. Auditory evoked potential index: A quantitative measure of changes in auditory evoked potentials during general anaesthesia. Anaesthesia. 1997;**52**(11):1030-1036

[69] Schraag S, Bothner U, Gajraj R, Kenny GN, Georgieff M. The performance of electroencephalogram bispectral index and auditory evoked potential index to predict loss of consciousness during propofol infusion. Anesthesia and Analgesia. 1999;**89**(5):1311-1315

[70] Tsurukiri J, Nagata K, Hoshiai A, Oomura T, Jimbo H, Ikeda Y. Middle latency auditory-evoked potential index monitoring of cerebral function to predict functional outcome after emergency craniotomy in patients with brain damage. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2015;**23**:80

[71] Krieger D, Adams HP, Schwarz S, Rieke K, Aschoff A, Hacke W. Prognostic and clinical relevance of pupillary responses, intracranial pressure monitoring, and brainstem auditory evoked potentials in comatose patients with acute supratentorial mass lesions. Critical Care Medicine. 1993;**21**(12):1944-1950

[72] Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science. 1977;**198**(4323):1264-1267

[73]  Kleinfeld D, Mitra PP, Helmchen F, Denk W. Fluctuations and stimulus-induced changes in blood flow observed in individual capillaries in layers 2 through 4 of rat neocortex. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**(26):15741-15746

[74]  Kim MB, Ward DS, Cartwright CR, Kolano J, Chlebowski S, Henson LC. Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. Journal of Clinical Monitoring and Computing. 2000;**16**(3):191-199

[75]  Peters J, Van Wageningen B, Hoogerwerf N, Tan E. Near-infrared spectroscopy: A promising prehospital tool for management of traumatic brain injury. Prehospital and Disaster Medicine. 2017;**32**(4):414-418

[76]  Vilkė A, Bilskienė D, Šaferis V, Gedminas M, Bieliauskaitė D, Tamašauskas A, Macas A. Predictive value of early near-infrared spectroscopy monitoring of patients with traumatic brain injury. Medicina (Kaunas, Lithuania). 2014;**50**(5):263-268

[77]  Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. Resuscitation. 2014;**85**(4):522-526

[78]  Rivera-Lara L, Geocadin R, Zorrilla-Vaca A, Healy R, Radzik BR, Palmisano C, Mirski M, Ziai WC, Hogue C. Validation of near-infrared spectroscopy for monitoring cerebral autoregulation in comatose patients. Neurocritical Care. 2017;**27**(3):362-369

[79]  Yokose N, Sakatani K, Murata Y, Awano T, Igarashi T, Nakamura S, Hoshino T, Katayama Y. Bedside monitoring of cerebral blood oxygenation and hemodynamics after aneurysmal subarachnoid hemorrhage by quantitative time-resolved near-infrared spectroscopy. World Neurosurgery. 2010;**73**(5):508-513

[80]  Smith SM, Vidaurre D, Beckmann CF, Glasser MF, Jenkinson M, Miller KL, Nichols TE, Robinson EC, Salimi-Khorshidi G, Woolrich MW, Barch DM, Uğurbil K, Van Essen DC. Functional connectomics from resting-state fMRI. Trends in Cognitive Sciences. 2013;**17**(12):666-682

[81]  Sporns O. Structure and function of complex brain networks. Dialogues in Clinical Neuroscience. 2013;**15**(3):247-262

[82]  Buzsáki G. The structure of consciousness. Nature. 2007;**446**(7133):267

[83]  Naghavi HR, Nyberg L. Common fronto-parietal activity in attention, memory, and consciousness: Shared demands on integration? Consciousness and Cognition. 2005;**14**(2):390-425

[84]  Massimini M, Ferrarelli F, Murphy M, Huber R, Riedner B, Casarotto S, Tononi G. Cortical reactivity and effective connectivity during REM sleep in humans. Cognitive Neuroscience. 2010;**1**(3):176-183

[85]  Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, Brichant JF, Bonhomme V, Maquet

P, Greicius MD, Laureys S, Boly M. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 2010;**113**(5):1038-1053

[86] Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: A functional magnetic resonance imaging study using propofol. The Journal of Neuroscience. 2010;**30**(27):9095-9102

[87] Ferrarelli F, Massimini M, Sarasso S, Casali A, Riedner BA, Angelini G, Tononi G, Pearce RA. Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(6):2681-2686

[88] Cao C, Slobounov S. Alteration of cortical functional connectivity as a result of traumatic brain injury revealed by graph theory, ICA, and sLORETA analyses of EEG signals. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2010;**18**(1):11-19

[89] Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, Franck G, Maquet P. Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. NeuroImage. 1999;**9**(4):377-382

[90] Kamiński MJ, Blinowska KJ. A new method of the description of the information flow in the brain structures. Biological Cybernetics. 1991;**65**(3):203-210

[91] Murphy M, Bruno MA, Riedner BA, Boveroux P, Noirhomme Q, Landsness EC, Brichant JF, Phillips C, Massimini M, Laureys S, Tononi G, Boly M. Propofol anesthesia and sleep: A high-density EEG study. Sleep. 2011;**34**(3):283-91A

[92] Astolfi L, de Vico Fallani F, Cincotti F, Mattia D, Marciani MG, Bufalari S, Salinari S, Colosimo A, Ding L, Edgar JC, Heller W, Miller GA, He B, Babiloni F. Imaging functional brain connectivity patterns from high-resolution EEG and fMRI via graph theory. Psychophysiology. 2007;**44**(6):880-893

[93] Gütling E, Gonser A, Imhof HG, Landis T. EEG reactivity in the prognosis of severe head injury. Neurology. 1995;**45**(5):915-918

[94] Logi F, Pasqualetti P, Tomaiuolo F. Predict recovery of consciousness in post-acute severe brain injury: The role of EEG reactivity. Brain Injury. 2011;**25**(10):972-979

[95] Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: A prospective study. Annals of Neurology. 2010;**67**(3):301-307

[96] Hartikainen KM, Rorarius M, Peräkylä JJ, Laippala PJ, Jäntti V. Cortical reactivity during isoflurane burst-suppression anesthesia. Anesthesia and Analgesia. 1995;**81**(6):1223-1228

# Cardiac Critical Care

# Current Perspectives on Cardiomyopathies

Nandita Mehta and Sayyidah Aasima tu Nisa Qazi

Additional information is available at the end of the chapter

## Abstract

Cardiomyopathy is a disease of the heart muscle that can affect any age group or gender and can be acquired or inherited. Its literal meaning is "heart muscle disease" and refers to the deterioration of the function of the myocardium for any reason. Cardiomyopathy affects the shape, function, and/or electrical system of the heart. Patients with cardiomyopathy can present to anaesthesiologists in emergency situations or as elective cases. The patients are usually not aware of their condition and may be diagnosed at the time of pre-anaesthetic check-up. Advanced cases are always a challenge to the anaesthesiologist as they are most commonly complicated by progressive cardiac failure. Patients with cardiomyopathy are often at risk of dysrhythmias or sudden cardiac death. This chapter describes the main features and perioperative management of patients with cardiomyopathies undergoing non-cardiac surgery. In general, the optimal anaesthetic management of patients with cardiomyopathy requires good preoperative assessment, close perioperative monitoring, suitable anaesthetic agents, optimal perioperative fluid management, and an overall stable hemodynamic status.

**Keywords:** anaesthesiologist, cardiomyopathy, anaesthetic management

## 1. Introduction

The first officially accepted definition of cardiomyopathy was given by WHO in 1980 which defined it as "heart muscle diseases of unknown cause" to differentiate cardiomyopathy from cardiac dysfunction which occurs due to known cardiovascular diseases such as hypertension, coronary artery disease, or valvular disease [1]. WHO reclassified cardiomyopathies in 1995 to include diseases of myocardium associated with cardiac dysfunction that were earlier excluded. They expanded this criterion in order to include all known causes of cardiomyopathy and is based on anatomical and physiological features. It includes three main types of cardiomyopathy: hypertrophic (HCM), dilated (DCM), and restrictive (RCM).

In 2006, American Heart Association (AHA) in their document entitled "Contemporary Definition and Classification of the Cardiomyopathies" defined cardiomyopathies as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are a part of generalised systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability." According to the new AHA classification, cardiomyopathies are divided into two broad groups: primary cardiomyopathies and secondary cardiomyopathies. Primary cardiomyopathies encompass those that are exclusively or predominantly confined to the heart muscle and are acquired, genetic, or of mixed origin. Secondary cardiomyopathies include the subset of multiorgan involving diseases, which cause involvement of the heart as a part of their pathophysiology. In spite of this detailed classification, some confusion may arise because some primary cardiomyopathies may have associated extra cardiac components while as a few secondary cardiomyopathies can affect the heart exclusively.

**Classification of primary cardiomyopathies:**

| | |
|---|---|
| Genetic | Hypertrophic cardiomyopathy |
| | Arrhythmogenic right ventricular cardiomyopathy |
| | Left ventricular noncompaction |
| | Glycogen storage disease |
| | Conduction system disease (Lenègre's disease) |
| | Ion channelopathies: long QT syndrome, Brugada syndrome, short QT syndrome |
| Mixed | Dilated cardiomyopathy |
| | Primary restrictive nonhypertrophied cardiomyopathy |
| Acquired | Myocarditis (inflammatory cardiomyopathy): viral, bacterial, rickettsial, fungal, parasitic (Chagas disease) |
| | Stress cardiomyopathy |
| | Peripartum cardiomyopathy |

**Classification of secondary cardiomyopathies:**

| | |
|---|---|
| Infiltrative | Amyloidosis |
| | Gaucher's disease |
| | Hunter's syndrome |
| Storage | Hemochromatosis |
| | Glycogen storage disease |
| | Niemann-Pick disease |

| | |
|---|---|
| Toxic | Drugs: cocaine, alcohol |
| | Chemotherapy drugs: doxorubicin, daunorubicin, cyclophosphamide |
| | Heavy metals: lead, mercury |
| | Radiation therapy |
| Inflammatory | Sarcoidosis |
| Endomyocardial | Hypereosinophilic (Löffler's) syndrome |
| | Endomyocardial fibrosis |
| Endocrine | Diabetes mellitus |
| | Hyper- or hypothyroidism |
| | Pheochromocytoma |
| | Acromegaly |
| Neuromuscular | Duchenne-Becker dystrophy |
| | Neurofibromatosis |
| | Tuberous sclerosis |
| Autoimmune | Lupus erythematosus |
| | Rheumatoid arthritis |
| | Scleroderma |
| | Dermatomyositis |
| | Polyarteritis nodosa |

European Society of Cardiology in 2008 introduced a classification in which they accommodated five specific types of cardiomyopathies along with their genetic involvement: dilated, hypertrophic, arrhythmogenic, restrictive, and unclassified [2]. They further divided them into familial (genetic) or non-familial (non-genetic).

The most recent classification known as the MOGE(S) classification system had been introduced which is based on phenotype and genotype an it incorporates information on structural and functional abnormalities (M), organ involvement (O), genetics (G), aetiology (E), and disease severity (S) associated with the condition [3]. However, it cannot be considered as complete as it does not include certain cardiomyopathies like postpartum cardiomyopathy or the risk of sudden death and is very complex to use. The MOGES classification is beyond the scope of this review so we do not discuss it here.

## 2. Pathophysiology

Cardiomyopathy itself can present as either systolic dysfunction or diastolic dysfunction, which in turn are both related to the ventricular dysfunction.

**Systolic dysfunction:** This type of dysfunction is mainly seen in dilated cardiomyopathy. The predominant pathophysiology is a global decrease in myocardial contractility, which in turn leads to reduction in left ventricular ejection fraction. In the initial phases, the heart tries to compensate this change by increasing the size of left ventricular cavity which allows for an improvement in stroke volume with an associated improved force of contraction. As the disease progresses, these compensatory mechanisms prove to be inadequate in maintaining the cardiac output, eventually leading to the failure of left heart.

**Diastolic dysfunction:** This is the most common type of dysfunction associated with the cardiomyopathies, occurring in HCM, RCM, and other types of cardiomyopathies. The main pathophysiology is impairment of filling of blood in the left ventricle, which leads to increase in the left ventricular filling pressures. During the beginning of the diastolic phase of a normal cardiac cycle, left ventricle undergoes the phase of Isometric relaxation (which is an energy dependent process) just before the start of left ventricle filling phase. This relaxation continues in the early left ventricular filling phase. The later part of the left ventricular filling is a passive process and depends on the compliance of the left ventricle. Diastolic dysfunction can be because of the impairment of any of the two phases: active relaxation or left ventricular compliance or a combination of the two. Ischaemia mainly affects the phase of isometric relaxation, while intrinsic myocardial pathologies including fibrosis or external restriction due to pericardial diseases may lead to a reduction in left ventricular compliance.

The main types of cardiomyopathy that we come across clinically in our day-to-day practice are:

- Dilated cardiomyopathy

- Hypertrophic cardiomyopathy

- Restrictive cardiomyopathy

- Arrhythmogenic right ventricular dysplasia

- Peripartum cardiomyopathy

Some other types of cardiomyopathy are known as "unclassified cardiomyopathy." Another type of cardiomyopathy known as Takotsubo cardiomyopathy has been recently listed and is also known as "stress-induced cardiomyopathy," or broken heart syndrome.

Therefore, we focus our attention towards the commonest types of cardiomyopathies in this chapter.

## 3. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is defined by cardiac enlargement with impaired systolic function of one or both ventricles. It is defined by the presence of:

**a.** Fractional myocardial shortening <25% and/or ejection fraction <45%.

**b.** Left ventricular end-diastolic diameter > 117% excluding any known cause of myocardial disease.

Familial DCM contribute about 20–48% of all DCM and can defined by

- the presence of two or more affected relatives with DCM meeting the above criteria or

- a relative of a DCM patient with unexplained sudden death before the age of 35.

The prevalence of DCM is 920/100,000 individuals and is common in Afro-Caribbean population. It is the commonest form of cardiomyopathy and is the third most common cause of congestive heart failure. DCM is the commonest indication for heart transplantation. In 30–40% patients, it is transmitted in an autosomal dominant fashion while in others it can be post viral or idiopathic. It can be of ischemic or nonischemic variety with ischemic type being related to atherosclerosis or CAD. The nonischemic variety may present itself secondary to the use of chemotherapeutic agents (doxorubicin and adriamycin), infections (Coxsackie virus, HIV, cytomegalovirus Chagas' disease, trichinosis, toxoplasmosis, Lyme disease, and leptospirosis), drug abuse (alcohol, heroin, cocaine, and methamphetamines), or as peripartum cardiomyopathy.

### 3.1. Pathophysiology

Dilated cardiomyopathy presents with a decrease in LV ejection fraction (LVEF) as described earlier, congestive heart failure (CHF) or as ventricular arrhythmias. Initially, the ventricle dilates to increase the force of contraction and stroke volume in order to maintain the cardiac output (Frank-Starling law); however, as the disease progresses, these compensatory mechanisms gradually fail, leading to the ventricular failure and ultimately failure to maintain the cardiac output (CO).

### 3.2. Signs and symptoms

The patients of dilated cardiomyopathy present with symptoms like dyspnea, orthopnea, fatigue, weakness, and oedema in the lower extremities. Physical findings are similar to those seen in CHF. Some patients complain of dyspnea on exertion that may look like angina pectoris. Patients may have jugular venous distention, crepitation on auscultation, resting tachycardia, audible s3 and s4 heart sounds, pulmonary oedema, and cardiomegaly. Mitral and/or tricuspid regurgitation may be audible clinically if the ventricular dilation is marked.

The ECG may show ST-T segment abnormalities, atrial fibrillation, intraventricular conduction defects, and PVCs. The echocardiography reveals dilated cardiac chambers, global hypokinesia, low EF/fractional shortening, raised LVEDP, mitral or tricuspid regurgitation and/or mural thrombi. Right-sided cardiac catheterisation using a Swan Ganz Catheter reveals a high

pulmonary capillary wedge pressure, high systemic vascular resistance, and a low cardiac output. Additional laboratory tests carried out may reveal raised brain natriuretic peptide levels.

### 3.3. Treatment

Management of DCM begins with lifestyle modifications such as adequate rest, weight control, low sodium diet, fluid restriction, stopping alcohol intake and smoking, and less physical activity during periods of cardiac decompensation.

*Medical management*: The patients of DCM are at increased risk of pulmonary and systemic thromboembolisation due to stasis of blood in the dilated hypokinetic cardiac chambers. Anticoagulation therapy with warfarin or dabigatran is often indicated in these patients. The risk of embolisation is the highest in patients with atrial fibrillation, severe left ventricular dysfunction, a previous history of thromboembolism, or echocardiographic evidence of a mural thrombus. Other medications like angiotensin-converting enzyme inhibitors and angiotensin antagonists, diuretics, beta blockers, vasodilators, digoxin, antiarrhythmics, and statins can be prescribed to keep the condition under control.

Patients with a LVEF <30% and an intraventricular conduction defect with wide QRS complex ≥130 ms may lack synchronised contraction of both ventricles. Resynchronisation of right and left ventricle with biventricular pacing using a cardiac resynchronisation therapy device (CRT-D) can restore synchronous contraction of both ventricles, shorten the QRS interval, decrease left ventricular size and improve systolic function, stroke volume and the overall survival rate of patients.

Heart transplantation is the definitive treatment and the most common indication for transplantation in patients with DCM for both adults and children. Patients that are likely to benefit highly from a heart transplant include patients who were previously very active, <60 years of age who show intractable symptoms of congestive heart failure despite optimal medical therapy.

### 3.4. Prognosis

Symptomatic patients with DCM who are referred to tertiary medical centres for care have a high 5-year mortality rate (50%). If the cardiomyopathy involves both the right and left ventricles, the prognosis is very poor. Haemodynamic abnormalities that predict a poor prognosis include:

- an ejection fraction <25%,
- pulmonary capillary wedge pressure > 20 mm Hg,
- cardiac index <2.5 L/min/m$^2$,
- pulmonary hypertension,
- systemic hypotension, and
- an increased central venous pressure.

### 3.5. Anaesthetic management for non-cardiac surgery

Any major surgeries on these patients can be associated with morbidity and mortality, therefore, requires planning. Optimisation of congestive heart failure (CHF) at least for a week before the planned surgery is advisable. In critically ill or patients undergoing a high-risk procedure or those in which CHF is not appropriately managed, intra-arterial BP line should be inserted preoperatively. Premedication should be tailored according to the patient's requirement and may include short acting anxiolytic and/or sedative. Regional anaesthesia or nerve blocks alone or in combination with general anaesthesia can help us achieve the set goals of anaesthesia with a minimal haemodynamic compromise. However, the ongoing anticoagulation therapy may limit the option of regional anaesthesia. American Society of Regional Anaesthesia (ASRA) guidelines must be strictly followed if the patient is on an anticoagulation therapy.

The goals of anaesthesia are to [4]:

- minimise any negative inotropic effect of anaesthetic drugs.

- prevent increases in afterload.

- maintain preload despite increased left ventricular end-diastolic pressure.

- maintain perfusion and control arrhythmias,

- avoid hypotension and tachycardia.

- avoid overdose of medications during induction as the circulation time of drugs is slow.

These patients can become haemodynamically unstable due to the depressant effect of anaesthetic agents, fluid shifts and ongoing blood loss, which add to the already poor myocardial function due the cardiomyopathy. Propofol, thiopentone and inhalational agents cause vasodilation and myocardial depression. Benzodiazepines like midazolam and nitrous oxide may cause cardiovascular depression. Etomidate, ketamine, and narcotics like opioids are the ones that have minimal adverse haemodynamic response. We need to use a balanced anaesthetic technique. Slow induction should be carried out. Response of induction agents may be delayed due to prolonged circulation time, so slow and titrated doses of anaesthetic agents should be administered. Additional doses may not be required.

Optimal pain management helps to maintain haemodynamic stability. Regional anaesthesia may be a source of excellent postoperative pain relief, reducing the episodes of sympathetically mediated tachycardia, and afterload increases.

*Monitoring*: In addition to basic monitoring, central venous pressure (CVP) monitoring allows us to measure preload and central venous saturation (ScVO$_2$). It provides for an access to administer inotropes and vasoconstrictors if needed. Direct intra-arterial pressure monitoring enables early identification of haemodynamic alterations by beat-to-beat measurement of BP. Pulmonary artery pressure monitoring is useful in patients undergoing high-risk or emergency surgery or those in whom large fluid shifts are anticipated. The role of noninvasive methods to estimate cardiac output as well as estimate global end-diastolic volumes, the extravascular lung water, and other indices if available are invaluable for assessing cardiac function.

Transesophageal echocardiography (TEE) is also helpful as it identifies causes of hypotension, response to fluid therapy or inotrope support, estimates preload, cardiac output, diastolic dysfunction, valve function, and regional wall motion abnormalities.

# 4. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy can be defined as abnormal LV thickening without chamber dilation that is usually asymmetrical, develops in the absence of an identifiable cause (e.g. aortic valvular stenosis[AS] and hypertension), and is associated with myocardial fibre disarray.

Hypertrophic cardiomyopathy (HCM) is very common and can affect people of any age group. It affects both sexes equally. It is a cause of sudden cardiac arrest and death in apparently healthy young people, including young athletes. HCM is a relatively common inherited disorder with an autosomal dominant pattern of inheritance with variable expression and has a prevalence of 1 in 500.

Defects of at least 11 genes and >1440 mutations sites demonstrate its genomic heterogeneity.

## 4.1. Pathophysiology

The underlying structural abnormalities in HCM are:

1. myocardial cell disarray where the cells are rearranged in a disorganised pattern as opposed to a normal parallel myocyte arrangement;

2. coronary microvasculature dysfunction due to increased wall to lumen ratio; and.

3. remodelling changes occurring in the heart.

These changes in HCM patients lead to diastolic dysfunction, impaired coronary reserve, supraventricular and ventricular dysrhythmias, and sudden cardiac arrest. Left ventricular remodelling can include fibrosis, focal, diffuse, asymmetric, or concentric hypertrophy, as well as decrease in the cavity size. The most common subtype of HCM presents as hypertrophy of the septum and the anterio-lateral free wall.

LV outflow tract obstruction (LVOTO) occurs in HCM, and initially it was proposed that the basal septal hypertrophy encroaching on the LVOT caused the obstruction of the tract. However, more recent studies have pointed towards the fact that during ventricular systole, flow against an abnormally positioned mitral valvular apparatus results in a Venturi effect on the anterior leaflet of the mitral valve and induces systolic anterior movement (SAM) of the anterior mitral valve leaflet. The mitral valve apparatus abnormalities can include hypertrophied papillary muscles touching the septum, elongated mitral leaflets, anterior displacement of papillary muscles, or anomalous insertion of the papillary muscle onto the anterior mitral leaflet. LVOTO can be precipitated or aggravated by increased contractility of the heart or tachycardia or decreased end-diastolic volume or systemic vascular (arterial) resistance. With HCM, incidence of diastolic dysfunction is more than LVOTO.

Myocardial ischaemia is present in patients with HCM, irrespective of the presence or absence of coronary artery disease. Myocardial ischaemia is precipitated by several factors including

- a mismatch between ventricular mass and coronary artery size,

- increased oxygen consumption due to hypertrophy,

- abnormal coronary arteries,

- decreased diastolic filling time,

- increased LVEDP compromising coronary perfusion, and

- the presence of a metabolic derangement regarding the utilisation of oxygen at the cellular level.

Supraventricular or ventricular dysrhythmias are relatively common in these patients due to the presence of disorganised cellular architecture, expanded interstitial matrix and myocardial scarring. They are the cause of incidence of sudden arrest in this group of cardiomyopathy.

### 4.2. Signs and symptoms

The clinical presentation of HCM varies widely. These patients can present early in their life with debilitating symptoms or can live for decades asymptomatically while some others die suddenly. The most frequent symptoms include dyspnea, dizziness, exercise intolerance, angina, syncope, and/or sudden death.

Physical examination may be normal at rest but may reveal a double apical impulse, gallop rhythm, a systolic murmur and thrill in the presence of functional LVOTO. It is rare, but some people with hypertrophic cardiomyopathy can suffer sudden cardiac arrest during a vigorous physical workout. The physical activity can trigger dangerous arrhythmias leading to sudden death.

The major risk factors for sudden cardiac death are:

- a family history of sudden death;

- unexplained syncope;

- extreme hypertrophy of the left ventricular wall (0.30 mm);

- non-sustained ventricular tachycardia (VT)

Electrocardiography (ECG) changes include left atrial (LA) enlargement, pathologic Q waves, high QRS voltage complexes, ST segment depression, and inverted T waves in at least two or more consecutive leads.

Echocardiography can easily demonstrate the presence of myocardial hypertrophy. Ejection fraction is usually >80%, reflecting the increase in force of contraction of the heart. Echocardiography can also assess the mitral valvular apparatus, the presence of mitral regurgitation, and the

presence of LVOTO by demonstrating turbulent flow across the aortic valve. Pressure gradients across the LVOT can be measured. Echocardiography is useful in evaluating diastolic function of the heart.

Invasive measures like cardiac catheterisation allow direct measurement of the increased left ventricular end-diastolic pressure and the pressure gradient between the left ventricle and the aorta.

The definitive diagnosis of HCM can be made by an endomyocardial biopsy and DNA analysis, but these diagnostic modalities are usually reserved for patients in whom the diagnosis cannot be established by non-invasive means.

### 4.3. Treatment

The varied clinical profile of HCM makes it difficult to establish some precise guidelines for the treatment of this condition. The treatment plan should be titrated according to individual patient requirements. However, it is prudent to mention that the patients who are at high risk for sudden death should receive aggressive treatment.

Medical management: Pharmacotherapy is aimed at reducing LVOTO, improving diastolic filling, and possibly decreasing myocardial ischaemia. A variety of medical therapies have been used in these patients with the aim of altering the natural history. These include β-blockers, $Ca^{2+}$ channel antagonists (verapamil or diltiazem), and disopyramide regimens, all of which seem to be effective as compared to no treatment in HCM patients. Most of these drugs used help HCM patients to improve their symptoms by reducing or eliminating the LVOT pressure gradient. These medications also reduce LVOTO during exercise by blunting the sympathetic response and are thus useful in treating the symptoms and attenuating the risk of sudden cardiac arrest. Atrial fibrillation often develops in these patients. It is associated with an increased risk of thromboembolism and congestive heart failure. Amiodarone is the most effective drug for prevention of repeated episodes of atrial fibrillation in these patients. Long-term anticoagulation is indicated in the patients with recurrent or chronic atrial fibrillation to prevent thromboembolic episode reducing the mortality and morbidity associated with it.

More recently, perhexiline, which augments myocyte energy supply, has been shown to improve diastolic dysfunction and symptomatology, but detailed studies are yet to follow.

**Alcohol septal ablation** [5]: Ethanol can be infused into the septal branches of the left anterior descending coronary artery and induce a targeted septal myocardial infarction (MI). Alcohol septal ablation is associated with some serious hazards, most common being the right bundle branch block, which has a post-procedural incidence of approximately 50%. Other complications include remote MI due to collateral circulation or an ethanol injection into the incorrect coronary, coronary dissection, ventricular septal rupture, heart failure, and heart block.

**Surgical management:** The American and European Colleges of Cardiology recommend myectomy in patients with:

1.  labile obstruction and peak LVOT pressure gradients ≥50 mm Hg during exercise or provocation and resting gradients >30 mm Hg and.

2.  NYHA class II through IV symptoms refractory to medical therapy.

Some patients may be candidates for implantable cardioverter-defibrillator (ICD) implantation while as principal surgical option is surgical myomectomy.

**Prognosis:** The overall mortality rate of HCM is 1% per annum. However, some patients at higher risk of sudden death as described before have an annual mortality rate of 5%.

**Patients undergoing non-cardiac surgery:** Most of the time, the patients with HCM are asymptomatic when they show up in the PAC clinic for elective surgeries. In the absence of signs and symptoms, the ECG findings may suggest that the patient has underlying HCM.

Initial patient evaluation should be aimed at determining the disease severity by assessing functional status of the patient, personal and family cardiac history, the presence or absence of cardiac and respiratory symptoms, history of rhythm disturbances, current medications, and previous strokes, or congestive heart failure history. During physical examination, all murmurs should be evaluated for dynamic changes with rest and exertion, and patients with murmurs that do not fulfil the criteria of a benign murmur should undergo an echocardiographic examination before surgery. Patients should be instructed to continue their rate controlling medications and maintain proper hydration preoperatively. Moreover, the presence of an automatic ICD and if it has been recently checked should be determined.

**Preoperative management:** A lot of patients with HCM may experience perioperative cardiac events like MI, congestive heart failure, severe hypotension, and supraventricular and ventricular tachydysrhythmias. Therefore, we need to focus on understanding the basic pathophysiology of the events and adjust our anaesthetic plans according to the patient needs.

In patients with HCM, preoperative administration of anti-anxiety medications may help to reduce anxiety and prevent the activation of anxiety-induced sympathetic response. Adequate preoperative intravenous fluid administration may help in preventing LVOTO and minimise the effect of positive pressure ventilation on central blood volume.

For patients who have an ICD in situ, the device should be turned off just before the surgery and an external defibrillator should be readily available and the ICD should be positively reactivated in the recovery room.

The anaesthetic goals are [4]:

- maintenance of sinus rhythm;

- reduction in sympathetic activity to reduce chronotropy and inotropy;

- the maintenance of systemic vascular resistance;

- maintenance of left ventricular filling.

Tachycardia, arrythmias, and decreases in afterload will exacerbate LVOTO and may cause haemodynamic deterioration. In addition to this, increases in contractility (chronotropy) and decreases in preload will accentuate LVOTO. Therefore, the principle of treatment for hypotension is volume expansion (including increasing preload in the Trendelenburg position) and use of drugs that increase systemic vascular resistance without a positive inotropic or chronotropic response (e.g. phenylephrine and vasopressin). Sympathetic response secondary to patient anxiety, intubation process, and surgical site incision and acute changes in preload, afterload, and contractility secondary to the pharmacological effects of anaesthetic agents, blood loss during surgery, and postoperative pain can precipitate haemodynamic collapse. DC cardioversion may be necessary in case of sudden onset of atrial fibrillation that is haemodynamically unstable.

Although both general and neuraxial anaesthesia can be used, it is important to have a clear understanding of the haemodynamic changes associated with each option. Depending on the route of the anaesthetic drugs chosen, close monitoring and titration of the medications affecting heart rate, preload, afterload, contractility of myocardium, and sympathetic activity are important. Neuraxial techniques may also be considered. In general, a slow controlled titration of medication via an epidural is preferred over a single dose spinal anaesthesia with the aim of maintaining preload and afterload and avoiding sympathetic stimulation. Regional anaesthesia can be an invaluable tool to manage postoperative pain and in turn prevent the activation of sympathetic response in these patients.

In addition to the standard American Society of Anaesthesiologists monitoring requirements, an intra-arterial catheter and/or non-invasive pulse plethysmographic variability (PPV) index monitor and central venous pressure (CVP) monitoring may be considered. The overall haemodynamic goals include maintaining the mean arterial blood pressure at >65–70 mm Hg to maintain coronary perfusion pressure to the subendocardium in the hypertrophied heart. The most useful monitoring tool for patients undergoing high-risk surgery is TEE. TEE can determine whether haemodynamic alterations are caused by hypovolemia, increased LVOTO or SAM, or LV systolic dysfunction.

**Postoperative management:** Patient with HCM should be continuously monitored in the postoperative room. All factors that activate a sympathetic response like pain, hypothermia, shivering, anxiety, hypoxia, and hypercarbia should be immediately addressed. The maintenance of euvolemia and prompt treatment of hypotension is very important.

## 5. Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a disorder of the myocardium that occurs due to increased myocardial stiffness (decreased compliance) that leads to impaired ventricular filling. Size of both ventricle chambers and systolic function usually remains normal or near-normal until later stages of the disease. RCM may arise as a result of either inherited or acquired predispositions and diseases or a combination of the both, and can broadly be classified as infiltrative, non-infiltrative, storage disease, and endomyocardial fibrosis. Restrictive

cardiomyopathy is prevalent in tropical regions of the world, where incidence of endomyo-cardial fibrosis is high. In non-tropical regions, idiopathic fibrosis is the common cause and is associated with increasing age. Other rare causes of RCM include amyloidosis, haemochromatosis, sarcoidosis, and eosinophilic endocarditis.

## 5.1. Pathophysiology

RCM is characterised by contracted stiff ventricles with progressive impairment of diastolic filling, leading to the haemodynamic problem of a low preload but high ventricular filling pressure. This pattern of diastolic dysfunction leads to dilation of the atria and elevation of mean atrial pressures, resulting in biventricular "backward heart failure" manifesting itself as pulmonary venous congestion leading to dyspnea as well as systemic venous pressure elevation resulting in peripheral oedema. Systolic function is preserved in most cases. However, in spite of intact systolic function, the restrictive pathology on true ventricular preload limit the stroke volume, resulting in low cardiac output and ultimately hypoperfusion of the tissues.

## 5.2. Signs and symptoms

RCM presents with signs and symptoms of both right and left heart failure. Patients complain of exercise intolerance because of diminished cardiac output. Patients often have a low volume pulse, an audible third heart sound, regurgitant murmurs, and a raised JVP with rapid X and Y descent that increases or fails to decrease on inspiration. Low blood pressures are often seen, complicating heart failure management. Pulmonary oedema is uncommon. Syncope occurs occasionally, often exertional, reflecting the limited ability of the heart to increase diastolic filling and is an ominous sign. Syncope may also be aggravated by antihypertensive medications. Concomitant autonomic neuropathy can precipitate orthostatic hypotension as can volume contraction from nephrotic syndrome.

Arrhythmias and conduction disturbances are frequent. Less frequent cardiac manifestations include dynamic LV outflow obstruction, often confused with hypertrophic cardiomyopathy; cardiac ischaemia caused by amyloid deposition in intramural coronary arteries; and intracardiac thrombosis caused by atrial wall standstill, with a risk for systemic embolisation.

The ECG may demonstrate conduction abnormalities. The chest X-ray shows signs of pulmonary congestion and/or pleural effusion, but cardiomegaly is absent. Echocardiography-based two-dimensional and Doppler are essential for determining diastolic dysfunction and for distinguishing patients with RCM from patients with restrictive physiology because of constrictive pericarditis. Echocardiography may also provide information to suggest a specific diagnosis such as the presence of regional wall motion abnormalities in a non-coronary distribution and aneurysms, which would raise the suspicion for cardiac sarcoidosis (CS). Cardiac magnetic resonance (CMR) imaging can aid in the diagnostic process, but the use should be determined on an individual basis. Endomyocardial biopsy (EMB) may be helpful for establishing a diagnosis in some cases. Ultimately, diagnosis of any of the RCMs relies on a constellation of clinical, laboratory, and imaging findings.

### 5.3. Management

Medical management: Treatment of RCM includes treating the underlying cause (if identified) and heart failure management. Diuretics are the mainstay of treatment to reduce volume overload. However, volume status in patients with RCM may be challenging to manage, as patients with RCM rely on high filling pressures to maintain cardiac output and excessive diuresis may result in tissue hypoperfusion. Digoxin must be used with great caution because it is potentially dysrhythmogenic in patients with amyloidosis. The use of β-blockers or calcium channel blockers to increase filling time or to manage arrhythmias should be carefully introduced, as some patients may be intolerant. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may also be considered, but the proof of benefit is lacking, and these agents may not be well tolerated. Anticoagulation is required in patients with atrial fibrillation, mural thrombus, or evidence for systemic embolisation and may be helpful in most patients because of propensity for thrombus formation in the left atrial appendage.

Surgical management: No corrective surgery has yet been proposed that would be 100% effective in improving the heart function in RCM. Advanced heart failure therapies, including cardiac transplantation, may be beneficial for selected patients. Heart transplantation is the only effective surgery that can be offered to the patients with restrictive cardiomyopathy. It may be the best option for those who are already symptomatic at the time of diagnosis or in whom reactive pulmonary hypertension exists. Left ventricular assist device (LVAD) therapy may be particularly applicable in patients with RCM as a bridge to transplant or as definitive therapy.

### 5.4. Patients posted for non-cardiac surgery

RCM presents a huge challenge for anaesthetists due to the high risk of morbidity and mortality. General anaesthesia causes vasodilation, suppresses the myocardium, and reduces venous return. The latter can be worsened by intermittent positive pressure ventilation resulting in cardiac arrest. Invasive arterial blood pressure monitoring and transesophageal echocardiography are useful in identifying the causes of cardiovascular instability [6].

The overall aims of anaesthesia are:

- sinus rhythm to be maintained if possible;
- to maintain adequate filling pressures;
- to maintain SVR in the presence of relatively fixed cardiac output.
- to manage electrolyte disturbances;
- to use anaesthetic agents with minimal cardiovascular effect like ketamine or etomidate.

## 6. Arrhythmogenic right ventricle cardiomyopathy

Arrhythmogenic right ventricle cardiomyopathy (ARVC) is characterised by structural abnormalities and cardiac dysfunction of mainly the right ventricle, but it can also involve the left

ventricle. It is a rare type of cardiomyopathy. It occurs if the muscle tissue in the right ventricle dies and is replaced by a scar tissue. This disrupts the pathway of the heart's electrical signals leading to arrhythmias.

ARVC usually affects teenagers or young adults. ARVC has a prevalence of 1 in 5000 among healthy young people. ARVC is seen in up to 20% of all causes of sudden death in young people. It is a complex genetic condition due to its genetic variation.

### 6.1. Pathophysiology

Histologically, the myocardial cells are replaced by the adipose and fibrous tissues. These alterations can form a re-entry electrical circuit triggering arrhythmias. ARVC usually starts as a localised disease with regional wall abnormalities. As the disease progresses, the right ventricle continues to lose the healthy tissue and dilates and becomes thin walled. Patients can develop right bundle branch block before they finally present with the symptoms of right ventricular failure between the fourth and fifth decades of life.

### 6.2. Signs and symptoms

Young patients often present with syncope, arrhythmia, cardiac arrest, or sudden death. The diagnosis of ARVC should be considered in:

- Young male athletes with cardiac symptoms.

- ECG showing ventricular tachycardia with left bundle branch block morphology.

- T-wave inversion in leads V1–V3.

- Premature ventricular complexes with left bundle branch block morphology.

- Spontaneous non-sustained ventricular tachycardia.

An accurate diagnosis of ARVC is important due to the high risk of drug-resistant arrhythmias and sudden cardiac death. The diagnosis can be established by myocardial biopsy, which shows adipocytes and fibrous tissue. However, these changes can be localised and may not be present at the exact site of biopsy. The availability of cardiac MRI and the gadolinium enhancement techniques are now fundamental in diagnosing ARVC eliminating the need for biopsies.

### 6.3. Management

The main aim of medical management is to prevent or reduce the risk of fatal arrhythmias.

- Sotalol, verapamil, and amiodarone can be used.

- Due to the recurrence of arrhythmias and drug resistance, continuous Holter monitoring, or an electrophysiological study may be required. Catheter ablation can be used as a palliative rather than a curative intervention. It is indicated in patients with monomorphic VT due to alocalised ARVC, with a drug-resistant arrhythmia, or with frequent intervention following ICD implantation [7].

- Early placement of an ICD may be lifesaving.

- In some exceptional cases, heart transplantation may be required.

## 7. Peripartum cardiomyopathy

Peripartum cardiomyopathy is a rare, dilated form of cardiomyopathy of unknown cause that occurs during the peripartum period, that is, the third trimester of pregnancy until 5 months after delivery. Peripartum cardiomyopathy (PPCM) is a major concern for anaesthetists and can occur in 1 in 10,000 pregnancies, but it is higher in subsequent pregnancies [8]. Patients may present with severe heart failure during the third trimester or up to 5 months postpartum. Many of these patients deliver via a normal vaginal delivery without complications; however, a few may require a Caesarean section.

**Risk factors** include maternal age > 30 years, multiparty, African descent, obesity, multiple pregnancy, hypertensive disorders, tocolytic therapy, viral infection, and cocaine use.

**Diagnostic criteria of peripartum cardiomyopathy:** The diagnosis of PPCM is usually made after the other causes of acute heart failure have been excluded. The criteria are:

- Heart failure developing towards the end of pregnancy or up to 5 months' postpartum

- Absence of another identifiable cause of cardiac failure

- Absence of cardiac symptoms or disease before late pregnancy

- Left ventricular dysfunction - defined as an EF <45% or reduced fractional shortening of <30%

### 7.1. Signs and symptoms

The patients usually present with sign and symptoms of heart failure: dyspnea, fatigue, and peripheral oedema. In early stages, these signs may mimic the presenting features of normal late pregnancy.

Echocardiography may show new onset of unexplained LV dysfunction and documentation of a new finding of dilated cardiac chambers with LV systolic dysfunction during the period surrounding parturition.

### 7.2. Treatment

The main aim of treatment is to relieve the symptoms of heart failure. Diuretics, vasodilators, and digoxin can be used effectively. During pregnancy, vasodilation is accomplished with hydralazine and nitrates. Intravenous immunoglobulin may have a beneficial effect. Thromboembolic complications are not uncommon, and anticoagulation may be required in most patients. Heart transplantation may be considered in patients who do not improve over time.

### 7.3. Prognosis

The mortality in this group of patients is as high as 30–60% due to pulmonary oedema and systemic embolisation with most deaths occurring mostly within 3 months of delivery.

### 7.4. Anaesthetic management

We have a very little literature regarding the anaesthetic management of PPCM yet. Optimum fluid management and avoiding myocardial depression are the major concerns for anaesthetists.

According to a few case reports, both general anaesthesia and neuraxial blocks have been successfully used for elective or emergency Caesarean section. Combined spinal epidural anaesthesia (CSE) is preferred by some. CSE causes less haemodynamic instability, has a higher success rate than epidural anaesthesia, results in better patient satisfaction, and provides good postoperative analgesia.

## 8. Takotsubo cardiomyopathy

Recently, Takotsubo cardiomyopathy has been described. Takotsubo cardiomyopathy is a rare condition of transient, reversible severe LV dysfunction and characterised by chest pain, dyspnoea, ST-T changes in ECG, ventricular arrhythmias, regional wall motion abnormalities on echocardiography, elevated cardiac enzymes, haemodynamic instability, pulmonary oedema, cardiogenic shock, or cardiac arrest without angiographic evidence of CAD.

### 8.1. Sign and symptoms

It is rare, usually occurs in postmenopausal women associated with stress and chest pain. ECG changes may include prolonged QTc interval which resolve in 1–2 days, ST-T changes, Q waves, resolve by discharge from hospital, and T inversion resolves slowly.

This condition is also known as apical ballooning syndrome and broken heart syndrome or stress-induced cardiomyopathy. Echocardiography shows akinesia of apical or midventricular segments leading to systolic dysfunction. The normal basal segments become hypercontractile, giving a ballooned-out appearance of the apical or mid-cavity segments. Ballooning may lead to altered spatial relationships between mitral leaflets and subvalvular apparatus, which may result in MR and dynamic LVOTO causing SAM.

Reversible myocardial ischaemia is seen on myocardial perfusion imaging, and positron emission tomography and magnetic resonance imaging confirm LV dysfunction. Biopsy may show lymphocytic infiltrates. Plasma levels of brain natriuretic peptide, catecholamines, cardiac enzymes and metanephrine are found to be elevated.

### 8.2. Management

Optimal therapy is yet to be defined [9]. Beta blockers, diuretics, and ACE inhibitor and vaso-dilators have been used. Adrenergic agonists and antiadrenergic therapy (beta adrenergic blockers or alpha 2 agonists) and QT prolonging medications are to be avoided.

### 8.3. Anaesthetic management

A principle anaesthetic goal is to avoid psychological and physical stress that could trigger acute cardiomyopathy in susceptible patients. Thorough patient counselling, effective premedication and preoperative beta blocker therapy before transfer to operating room are highly effective.

Laryngoscopy, intubation, extubation, emergence, and inadequate postoperative pain control may cause a sympathetic response and increase catecholamine levels, so an optimal anaesthesia/analgesia is required in these phases. It is suggested that regional anaesthesia may be beneficial, but adequate studies to support this theory are not available.

It is unclear whether administration of inotropic drugs to treat systolic dysfunction is harmful. Inotrope of choice remains unclear, though Milrinone, aphosphodiesterase inhibitor, and a calcium sensitizer, levosimendan are suggested. Mechanical support of circulation with IABP or LVAD is an option to tide over periods of crisis. Beta blocker therapy may not be haemodynamically tolerated or could be potentially hazardous. Beta agonists should be avoided or used carefully, vasopressors may be used and supportive treatment for CHF should be instituted. LV dysfunction resolves within 2–4 weeks. Most cases recover spontaneously with a mortality risk of 0–8%.Recurrence occurs in 2–5% cases [10].

## 9. Intensive care unit management

When a person is admitted with a diagnosis of cardiomyopathy, the main aims of therapy whether in the intensive care or coronary care unit are, to reduce the workload of the heart and to improve the pumping ability of the heart. This can be achieved with the help of drugs such as inotropes, diuretics, ACE inhibitors, beta blockers, calcium channel blockers, and so on, which aids in improving the pumping action of the heart muscle and treatment to ensure the proper volume of blood in the body.

Treatment of the patients in the intensive care unit depends not only on the type and the severity of cardiomyopathy but also condition of patient. Treatment may include conservative management with drugs, implantation of pacemakers, defibrillators for those prone to fatal heart rhythms, ventricular assist devices or extracorporeal membrane oxygenators for severe heart failure, or ablation for recurring dysrhythmias that cannot be managed by drugs or cardioversion. The goal of management in the intensive care unit is often symptomatic, and some patients may eventually require a heart transplant.

## 10. Conclusion

Nowadays, cardiomyopathies are being identified increasingly as a result of improved means of detection with echocardiographic examination and an increase in the ageing population group. In addition, the presentation of this disease is varied. It may be sudden or already well known to the patient. Anaesthesia administration for patients with cardiomyopathy can lead to perioperative morbidity and mortality during elective or, more importantly in emergency surgeries. Therefore, anaesthesia and postoperative care have to be carefully titrated, planned, and monitored for every patient, for which we need a thorough understanding of the pathophysiology of cardiomyopathies. The best approach would be a multidisciplinary team that includes anaesthetists, cardiologists, and surgeons. As anaesthesiologists, we have to expand our horizon from operating room to ICU with a thorough understanding of non-invasive and invasive monitoring methods and a basic knowledge of transthoracic echocardiography.

## Abbreviations

| | |
|---|---|
| AHA | American Heart Association |
| ARSA | American Society of Regional Anaesthesia |
| ARVC | arrhythmogenic right ventricular cardiomyopathy |
| AS | aortic stenosis |
| CAD | coronary artery disease |
| CHF | congestive heart failure |
| CMR | cardiac magnetic resonance |
| CO | cardiac output |
| CTR-D | cardiac resynchronisation therapy device |
| CVP | central venous pressure |
| DCM | dilated cardiomyopathy |
| EF | ejection fraction |
| EMB | endomyocardial biopsy |
| HCM | hypertrophic cardiomyopathy |
| IABP | intra-arterial blood pressure |
| ICD | implantable cardioverter-defibrillator |

| LA | left atrium |
| LV | left ventricle |
| LVAD | left ventricular assist device. |
| LVEDP | left ventricular end-diastolic pressure |
| LVEF | left ventricular ejection fraction |
| LVOTO | left ventricular outflow tract obstruction |
| NYHA | New York Heart Association |
| PPCM | peripartum cardiomyopathy |
| PPV | pulse plethysmographic variability |
| PVC | premature ventricular complex |
| RCM | restrictive cardiomyopathy |
| SAM | systolic anterior moment |
| $ScVO_2$ | central venous oxygen saturation |
| SVR | systemic vascular resistance |
| TEE | trans esophageal echocardiography |
| VT | ventricular tachycardia |
| WHO | World Health Organisation |

## Author details

Nandita Mehta* and Sayyidah Aasima tu Nisa Qazi

*Address all correspondence to: drnanditamehta@gmail.com

Department of Anaesthesia and Critical Care, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, India

## References

[1] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;**113**:1807-1816

[2] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: A position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. European Heart Journal. 2008;**29**:270-276

[3] Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, et al. The MOGE(S) classification for aphenotype-genotype nomenclature of cardiomyopathy: Endorsed by the World Heart Federation. Journal of the American College of Cardiology. 2013;**62**:2046-2072

[4] Stoelting RK, Dierdorf SF. Cardiomyopathy. In: Stoelting RK, editor. Anaesthesia and Coexisting Disease. 3rd ed. New York: Churchill Livingstone; 1993. pp. 97-102

[5] Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, Maher AR, Kaur K, Taylor J, Henning A, Ashrafian H, Watkins H, Frenneaux M. Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. Circulation. 2010;**122**:1562-1569

[6] Ammash NM, Seward JB, Bailey KR, et al. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. Circulation. 2000;**101**:2490-2496

[7] Basso C, Corrado D, Bauce B, et al. Arrhythmogenic right ventricle cardiomyopathy. Circulation. Arrhythmia and Electrophysiology. 2012;**5**:1233-1246

[8] Shnaider R, Ezri T, Szmuk P, et al. Combined spinalepidural anesthesia for cesarean section in a patient with peripartum dilated cardiomyopathy. Canadian Journal of Anesthesia. 2001;**48**:681-683

[9] Banerjee S. Takotsubo cardiomyopathy: A review. JSM Atherosclerosis. 2016;**1**:1011

[10] Littlejohn FC, Syed O, Ornstein E, Connolly ES, Heyer EJ. Takotsubo cardiomyopathy associated with anesthesia: Three case reports. Cases Journal. 2008;**1**:227

*Edited by Rıza Hakan Erbay*

Knowledge of intensive care medicine is growing logarithmically. In addition, intensive care units and their number of beds are increasing in hospitals. Nowadays, the average human life is prolonged due to the growth of medical knowledge and skills. Intensive care units, both as a cause and as a consequence of long-life expectancy, are increasingly important. This book contains current topics on intensive care such as critical care for neonatal, neurological, and cardiological patients; fluid management in these patients; and intensive care infections. We wish the readers find this book to be helpful.