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Part VIII Humanization

Acronyms

ABA	American Board of Anaesthesiologists
ACCP	American College of Chest Physicians
ACHF	Advanced congestive heart failure
ACS	American College of Surgeons
AECC	American–European Consensus Conference
AEDs	Automatic external defibrillators
AKI	Acute kidney injury
ALF	Alveolar lining fluid
AND	Allow natural death
APACHE	Acute physiology and chronic health evaluation
APACHE II	Acute physiology and chronic health evaluation II
APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
ATIII	Antithrombin III
AUC/MIC	Area under the concentration-time curve and the minimum inhibitory concentrations
BAL	Bronchoalveolar lavage
BCs	Blood cultures
BG	1,3-beta-d-glucan antigen
BLUE-protocol	Bedside lung ultra sound in emergency
BMI	Body mass index
BNP	Brain natriuretic peptide
BSIs	Bloodstream infections
BTE	Biphasic truncated exponential
CA	Cardiac arrest
CAGTA	Candida albicans IFA IgG for germ tube antibody detection
CA-MRSA	Community-acquired MRSA
CDC	Centers of disease control and prevention
CFU	Colonies forming units
CHF	Congestive heart failure
CHVVVH	High volume continuous veno-venous hemofiltration
CI	Confidence interval
CO	Cardiac output

COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPIS	Clinical pulmonary infection score
CPP	Coronary perfusion pressure
CPR	Cardiopulmonary resuscitation
CRRT	Continuous renal replacement therapy
CRRT	Continuous renal replacement treatments
CTARP	Cambridgeshire trauma audit and research project
CUH	Cambridge university hospitals
CVP	Central venous pressure
CVVH	Continuous veno-venous hemofiltration
CXR	Chest radiograph
DFT	Defibrillation threshold
DM	Diabetes mellitus
DNR	Do-not-resuscitate
DPAHC	Durable power of attorney for health care
DVT	Deep venous thrombosis
EAPC	European association for palliative care
EBM	Evidence based medicine
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
EEG	Electroencephalography
EFISG	European Fungal Infection Study Group
EGDT	Early goal directed therapy
ELISA	Enzyme-linked immunosorbent assay
EMRs	Electronic medical records
EMS	Emergency medical service
EoE	East of England
EORTC/MSG	European Organization for Research in the Treatment of Cancer/Mycosis Study Group
ER	Emergency rooms
ERC	European Resuscitation Council
ESBL	Extended-Spectrum-β-Lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EtCO2	End-tidal CO_2
EUSOS	European surgical outcomes study
FALLS-protocol	Fluid administration limited by lung sonography
FEVI	Forced expiratory volume (in 0.1 sec)
FRC	Functional residual capacity
GCS	Glasgow coma scale
GERD	Gastroesophageal reflux disease
GM	Galactomannan
GUCH	Grown up congenital heart disease

HAP	Hospital-acquired pneumonia
HCAP	Health care-associated pneumonia
HF	Heart failure
HPE	Hemodynamic pulmonary edema
HPS	Human patient simulator
hrAPC	Human recombinant activated protein C
IABP	Intra-aortic balloon pump
IAP	Intraabdominal pressure
IC	Invasive candidiasis
ICD	Implantable cardioverter-defibrillator
ICPCN	International children's palliative care network
ICU	Intensive care units
IFD	Invasive fungal diseases
IFIs	Invasive fungal infections
Ig	Immunoglobulin
IHD	Intermittent haemodialysis
IL-1	Interleukin 1
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-8	Interleukin 8
ILCOR	International Liaison Committee on Resuscitation
IMPaCCT	International meeting for palliative care in children, Trento
IRT	Intermittent renal treatments
IS	Incentive spirometry
ISS	Injury severity score
IT	Information technology
LAS VEGAS	Local assessment of ventilatory management during general anaesthesia for surgery
LUCI-FLR	Lung ultrasound in the critically Ill favoring limitation of radiographies
LUS	Lung ultrasound
LWMH	Low weight molecular heparin
MAP	Mean arterial pressure
METs	Metabolic Equivalent
MIC	Minimum inhibitory concentration
MIE	Mini-invasive esophagectomy
MITS	Minimally invasive thoracic surgery
MODS	Multiple organ dysfunction syndrome
MRSA	Meticillin-resistant *S. aureus*
MSSA	Methicillin-susceptible *S. aureus*
MTC	Major Trauma Centre
MW	Molecular weight
NAO	National Audit Office
NCAG	Clinical Advisory Groups
NCCN	National comprehensive cancer network

NHLBI	National Heart, Lung and Blood Institute
NHPCO	National Hospice and Palliative Care Organization
NHS	National health service
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
Noisy PSV	Noisy pressure support ventilation
NOTES	Natural orifice transluminal endoscopic surgery
NSQIP	National surgical quality improvement program
OCS	Order communicating system
OE	Open esophagectomy
OSA	Obstructive sleep apnea
PAC	Pulmonary artery catheterisation
PACS	Picture archiving communication system
PAF	Platelet activating factor
PAN	Polyacrilonytrile
PAP	Plasmin/antiplasmin
PBS	Protected specimen brush
PBW	Predicted body weight
PCA	Palliative care Australia
PCAS	Post-cardiac arrest syndrome
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PCT	Procalcitonin
PEA	Pulseless electrical activity
PEEP	Positive end-expiratory pressure
PERISCOPE	Prospective evaluation of a risk score for postoperative pulmonary complications in Europe
PICU	Pediatric intensive care unit
PIRO	Predisposition, infection, host response, and organ dysfunction
POEM	Peroral endoscopic myotomy
PPCs	Postoperative pulmonary complications
PRF	Postoperative respiratory failure
PROVHILO	Protective Ventilation using high versus low positive end-expiratory pressure
PSB	Protected specimen brush
PSDA	Patient self-determination act
PSV	Pressure support ventilation
PTA	Polymyxin E, tobramycin, and amphotericin B
PVR	Pulmonary vascular resistance
Qb	Blood flow
Qf	Ultrafiltrate flow
RCT	Controlled randomized trial
RIFLE	Risk injury Failure, Loss and End-stage kidney disease
RLB	Rectilinear biphasic
ROSC	Restoration of spontaneous circulation

RR	Risk ratio
RRT	Replacement treatments
SAPS	Simplified acute physiology score
SCS	Simple cardiac sonography
SDD	Selective decontamination of the digestive tract
SIRS	Systemic inflammatory response syndrome
SLED	Slow low efficiency dialysis
SLIP score	Surgical lung injury predictor score
SNS	Social network system
SOD	Selective oropharyngeal decontamination
SOFA	Sequential organ failure assessment
SOPs	Standard operative procedures
SSC	Surviving sepsis campaign
SVR	Systemic vascular resistance
TA	Tracheal aspirate
TARN	Trauma audit and research network
TAT	Thrombin/antithrombin
TEE	Transesophageal echocardiogram
Tele-ICU	Telemedicine ICU
TF	Tissue factor
TH	Therapeutic hypothermia
TIA	Transient Ischemic attack
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
TNF-α	Tumour necrosis factor-α
TNO	Trauma network office
TOE	Transoesophageal echocardiography
TTI	Transthoracic impedance
TU	Trauma unit
UF	Ultrafiltrate
VAE	Ventilator-associated event
VAP	Ventilator-associated pneumonia
VATS	Video-assisted thoracoscopic surgery
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO	World Health Organization

Part I
Advances on Intensive and Critical Care Medicine

Combining Clinical Practices and Technology in Critical Care Medicine

1

Younsuck Koh

1.1 Introduction

The intensive care unit (ICU) is a place in which various advanced medical technologies are gathered for the monitoring and management of severely ill patients. Medical technology now permits a more precise and timely diagnosis and treatment than when the modern era of intensive care began. These days, we could not contemplate an ICU without the relevant medical tools and equipment. As intensive care becomes more complicated due to the increased intricacies of critical illnesses, the relevant state-of-the-art medical technologies have also been evolving to meet the requirements of intensive care providers and patients.

Medical technologies have now expanded beyond the ICU. Clinical simulation systems provide safe clinical skill training opportunities so that patients need not be subjected the training needs of resident physicians on rotation in an ICU. Moreover, with the integration of current digital technologies into medicine, traditional medical practices have been changing more than expected.

However, the latest medical technologies are frequently expensive, and the clinical outcomes do not always justify the expense. In this regard, deciding on the technologies that should be adopted and determining how to integrate them into clinical practice for appropriate critical care has become an important issue. Another concern is that a high dependence on technology will lead to deterioration in clinical reasoning abilities and the skill levels of critical care trainees. Hence, the debate on the validity and cost-effectiveness of specific new technologies

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seems set to continue in response to the high costs of critical care. This chapter discusses the positive and negative aspects of medical technologies, and the optimal combination of clinical practice and technology that will deliver the best critical care.

1.2 The Technologies Used in Critical Care Medicine

Medical technology is defined as any intervention that may be used for health care. It broadly includes medical equipment, information technology, clinical skills, and healthcare services (Fig. 1.1). Medical technology is developed in tandem with a relevant clinical necessity, with an idea generated at the patient bedside often contributing to this advance. The invention of the stethoscope is a typical example of an ideal coupling of clinical skills and technology. The incessant development of medical technology performs a crucial role in minimizing medical errors and enhancing the quality and effectiveness of care.

Some technologies broaden medical knowledge, improve clinical performance, and lead to the further development of relevant technologies. Radiological imaging and electrical recording on the surface of the human body are regarded as milestone technologies in medicine. Some medical technologies have become essential tools for critically ill patients, such as artificial renal dialysis, mechanical ventilation, and the defibrillator, which are now first-line life saving devices in the ICU. The role of ultrasonography has also been expanding in the ICU. In addition, sometimes a newly introduced technology stimulates new clinical skill development. The pressure support ventilation (PSV) mode is the typical example. The PSV mode was not adopted until critical care physicians recognized its usefulness as a weaning mode, several years after its initial introduction.

An increased understanding of a clinical phenomenon permits physicians to reevaluate daily applications of technologies. For example, an improved understanding of underlying ventilator-associated lung injury led to a modification of

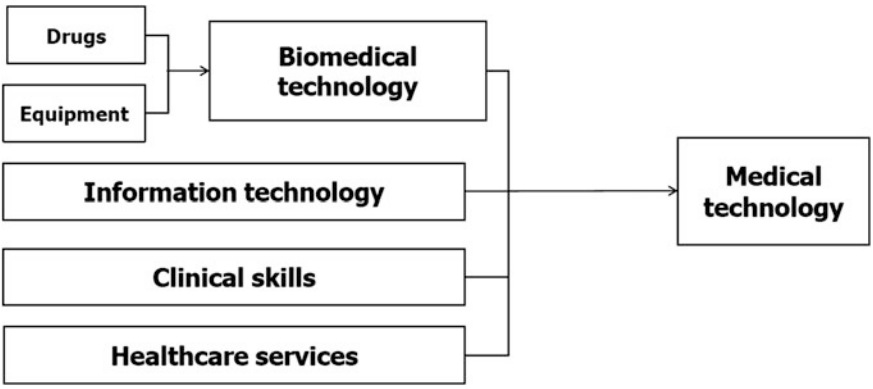

Fig. 1.1 The spectrum of medical technology

ventilation strategies—without equipment change—in cases of acute respiratory distress syndrome (ARDS) [1]. The proven efficacy of low tidal ventilation in the treatment of ARDS led investigators to discourage the use of high-frequency ventilation in adult ARDS patients [2]. Recent advances in extracorporeal membrane oxygenation equipment have enabled a previous poor reputation to be overcome, and this technology now shows efficacy in treating ARDS [3].

1.3 The Influence of Digital Technologies on Critical Care Medicine

The introduction of digital technology has opened up new horizons in clinical practice. Computed tomography, as a representative example of a digitized diagnostic tool, has improved our diagnostic capabilities and extended our understanding of many critical illnesses. The impact of digitized healthcare information technology (IT) on medicine seems to be greater than expected. Through the digitization of clinical data, data storage, and retrieval has become easier, quicker, and more accurate. Electronic medical records (EMRs), picture archiving communication systems, and order communicating systems (OCSs) are examples of

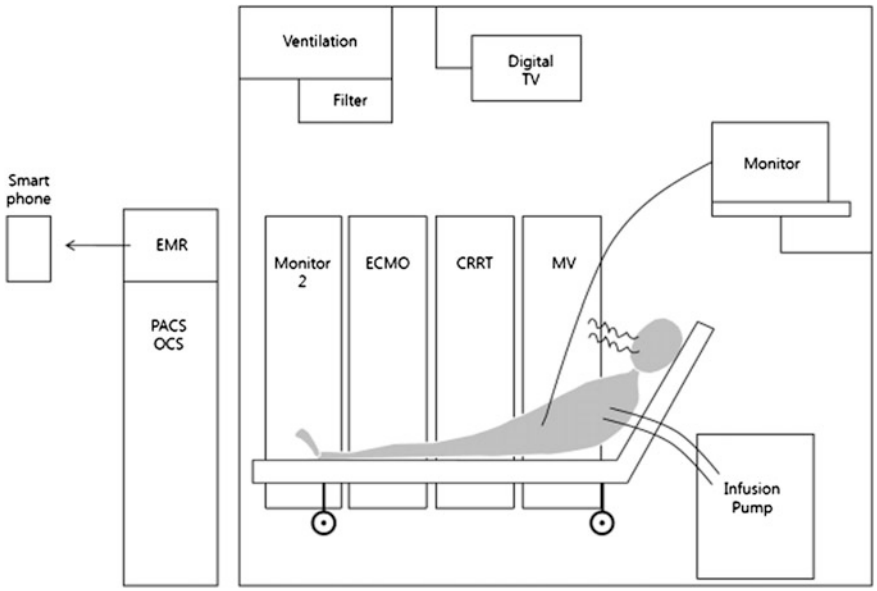

Fig. 1.2 An example of a digitalized ICU environment. Monitoring data from a patient monitor or mechanical ventilator can be automatically transferred to the EMR system.: *CRRT* continuous renal replacement therapy; *ECMO* extracorporeal membrane oxygenation; *EMR* electric medical record; *MV* mechanical ventilation; *OCS* order communicating system; *PACS* picture archiving communication system

recent digital technologies that are increasingly being adopted by hospitals worldwide. EMRs have improved the accessibility, legibility, and storage of patient records. These health ITs have been reported to reduce medication errors and health care costs. A cross-sectional study of urban hospitals in Texas measured the level of automation of each hospital based on physician interactions with the information system, which included medical records, test results, order entries, and decision support. The investigators found in this multihospital study that hospitals with automated notes and records, order entries, and clinical decision support had fewer complications, lower mortality rates, and even lower costs [4].

The ICU is a very good setting to exploit the potential benefits of IT. In fact, IT technology now plays a role in every aspect of the work of a modern ICU, supporting both clinical decisions and care (Fig. 1.2). By connecting to a relevant website through handheld digital equipment or even a smart phone, clinicians can now obtain clinical references that are urgently needed for decision making at the bedside. Through the implementation of management guidelines based on sound medical evidence, the OCS of a hospital can amend essential orders that have been missed and continuously monitor order compliance.

Some monitoring systems, such as a continuous hemodynamic monitor, can give advice on patient management based on specific algorithms. Clinical information can be simultaneously shared between physicians at different hospitals if they are equipped with a common interface for data communication. Telemedicine ICU (Tele-ICU) is an electronic means to link ICUs at different locations, which then assists in medical decision making. Given the shortage of intensive care physicians, Tele-ICU systems could be an alternative mechanism for physicians to manage a larger number of critical care patients and to enable 24 h, 7-day ICU coverage [5]. Robotic support is also now being used as a mobile monitoring device in remote locations. Telemedicine seems to make possible of home-bound ICU care in near future.

As digital technology can generate large data sets, the valuable data could be used by variable stakeholders related to public health care. In the public health sector in the United States, the sharing of large data sets for better critical care policy development has been already initiated. The problem to be encountered is inadequate staffing, training, and resources for data collection [6].

1.4 The Negative Influence of Medical Technologies on Intensive Care Medicine

It has been anticipated in some quarters that advanced technology will provide us with more accurate clinical information and better clinical guidance. The preference of physicians for high technology has also been changing their diagnostic approaches. Even experienced chest physicians depend more on chest-computed tomography than on simple chest X-rays to reduce possible medical errors. Increased medical malpractice disputes are one cause of the increased dependence

of physicians on advanced technology. However, the increased adoption of advanced technology has resulted in an increase in medical expenses. The value of this has generally not been well established in terms of patient outcomes and cost-effectiveness.

Another practical problem relates to the differences in the results obtained when using different equipment that has been developed for the same purpose. These discrepancies may occur due to the different hypotheses and algorithms inherent in the individual equipment. In a study to compare updated hemodynamic monitoring equipment, similar mean CO values were obtained [7]. However, these values often trended differently in response to therapy [7]. The algorithms contained in different devices are based on a particular hypothesis, which may not match the specific condition of the patient in question. Given that clinical decisions have to be made frequently in an ICU setting, trend differences may become a considerable problem for critical care physicians. Nurses can also experience difficulties with the implementation of new and obtrusive technology at the bedside [8].

Organizational issues can also occur when implementing novel technology in the ICU. Physicians may not like to use unfamiliar new technology, and the process of adopting new technology frequently requires a reported benefit, such as in cost or patient handling, and the agreement of other stakeholders. Moreover, high-level technology does not always go hand-in-hand with the interpersonal approaches often required of care providers for more fragile patients and their families. Instead of frequent visits to the critically ill patient's bed, care providers can more easily refer to the clinical information obtained by different devices.

The clinical reasoning ability of a trainee could also be hampered by a high dependence on the management algorithm used in updated monitors. It was reported in an ICU-based cohort study that copying of EMRs among attending and resident physicians was common [9]. Easy copy-and-pasting of the EMR could also lead to deterioration in the clinical reasoning process or in the new data gathering of the related healthcare providers.

Another difficulty encountered by intensivists in the digital technology era is related to family discussions. Patients' families can gather more relevant clinical information through the internet than ever before. However, their incomplete medical information could result in a misunderstanding of the care providers' decisions, resulting in a deterioration of the rapport between care providers and families.

An appropriate audit for an improved patient outcome through IT systems is a highly valuable exercise, as explained above. However, a misused performance measurement by an authorized organization can negatively influence a physician's autonomy in clinical decision making. Currently, medical insurance organizations and health policy makers have begun to measure performance using their own scales, which are based on digitized clinical information and reflect the relationship between the clinical outcome and the medical expense.

1.5 The Optimal Combination of Medical Knowledge and Skills, and Advanced Medical Technologies for Critical Care Medicine

Although effective and proven guidelines can improve patient outcomes [10], clinical guidelines are fully applied to only small groups of patients, as shown by studies into the compliance of low tidal volume strategies with ARDS [11] and surviving sepsis guidelines [12]. In a previous 1-day audit survey into the performances of designated guidelines in French adult ICUs, the clinical guidelines were found to have been fully applied at the bedsides of only 24 % of patients [13]. These results underline the need to both improve the process of implementation and obtain immediate feedback on missed performances. The inherent instant monitoring of IT applications and the ability to immediately respond to physicians' orders has the potential overcome barriers to guideline implementation.

Although the effect of Tele-ICU on patient outcome has not yet been validated, telemedicine appears to be one solution for the 24 h/7-daycoverage required of an ICU. One study has shown that Tele-ICU coverage is associated with a lower ICU mortality and length of stay, but not with lower in-hospital mortality or hospital length of stay [14]. The combination of telemedicine and internet technology may permit the development of home-based monitoring systems for chronically ill patients. Such e-health technology may then enable the proactive management of critically ill patients before their arrival at the hospital. A retrospective analysis has shown that perceived emergencies in nonhospitalized patients occur commonly but require minimal emergent intervention [15]. Early appropriate intervention in such a fragile patient can reduce the length of hospital stay and medical expenses and obtain a better outcome through a simple home-based IT system [16].

Another potential use of IT in the ICU resides in its role as a communication facilitator. If well-designed, e-health technology could positively contribute to intensive care medicine through the enhancement of bilateral communication between healthcare providers and patients' families. It could enable patient-centered ICU development through communication enhancement via various IT tools. It permits the patient's family members that cannot regularly visit the ICU to see the EMR through a social network system (SNS), as long as the healthcare providers and government regulations permit a log into the EMR site for these individuals. The patient's family can also contribute to the management of the patient by providing information that may be missed during history taking. By letting the patient's family follows the decision processes of the ICU care providers through the SNS, these process may be better facilitated. End-of-life care could also be better performed through e-health technologies. Furthermore, the advance directives of patients could be recorded and stored ahead of time at an officially endorsed site.

Through the various levels of medical information on the internet, including hospital homepages, patients can receive undesirable attributions and biased viewpoints against a certain hospital or certain doctors. The impact of this can be

worldwide in the current era of medical tourism, where patients search for cheap, but good quality care. To cope with such a detrimental influence of e-health technology, healthcare stakeholders should strengthen their sensitivity to relevant medical ethical considerations. Intensive care physicians should carefully consider what they can do and what they should do. These physicians should make balanced decisions about cost-performance and ethical approaches to the implementation of newly developed medical technologies when treating a critically ill patient. In resource-limited ICUs, more evidence-based approaches should be performed to select essential and affordable technologies.

We know that better clinical outcomes can be achieved through both relevant medical knowledge and the appropriate technological support. The importance of careful clinical observation and an experienced integrated clinical decision could not be underestimated even in the high-technology ICU care environment infuture. The truth of medicine is that many diagnoses can be made based on history alone or based on history and physical examination. Expensive tests often confirm what is found during the history and physical examination. Therefore, the importance of adequate staffing of critical care providers together with a well-prepared critical care training system should not be underestimated by hospital administrators and health policy makers.

It is becoming increasingly common for government bodies, healthcare providers, funders, and consumers to seek measures of the quality of critical care. It must be ensured that the quality of the ICU data is sufficiently high to enable stakeholders to confidently use quality of care measures. For better data gathering, associated resource enhancement, including updated technology and improved staffing and training, is needed. Furthermore, the development of an internationally applicable common interface for ICU patient data exchange is urgently required.

1.6 Conclusion

Technology and medical practices will always change and adapt over time. The most desirable advances in medical technology would be to simplify complex procedures and make them less error prone. Medical technology also has to be further focused on reducing the cost of public health and improving ICU care quality. To achieve these goals, physicians should enter into effective partnerships with the technology developers, who are often not familiar with the requirements of an ICU. In addition, all of these processes should be performed in ethical ways to avoid undesirable conflicts of interest.

Critical care providers will be challenged to keep pace with rapidly advancing technologies and their diverse roles in ICU care. To cope with these requirements, critical care providers, hospital administrators, and healthcare policy makers should look beyond traditional medical practice, seeking lessons on quality

assurance from industry (e.g., aviation). Modern ICU quality improvement initiatives that aim to ensure evidence-based best practice could be achieved through the balanced coupling of clinical practice and technology in critical care. In medical resource-poor countries, the adoption of a new technology in individual ICUs should be based on its known efficacy, user consensus, and the guidance of the team leader for better ICU care. Its usefulness should be confirmed by its cost and benefit aspects compared with comparable tools.

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Ultrasound in Critical Care: A Holistic Discipline

2

Daniel A. Lichtenstein

2.1 Introduction

Intensive care, a 60 year old discipline, has always tried to improve patient's care using and *adapting* tools from other specialties. Ultrasound is one of them, recently discovered although long available [1]. In critical care, François Jardin used it for cardiac imaging in substitution to usual tools such as Swan-Ganz catheter [2]. From this beginning, by successive extensions, ultrasound became a topic in congresses of many disciplines (intensive care, anesthesiology, emergency medicine, a.m.o.). Countless young doctors use it daily, not all aware of how it came on their hands. We were just wondering what was the main reason for being given an award prize at the APICE congress.

2.2 A Begin Before the Current Rush?

In 1983, a student was kindly asked to transport a lady to the ultrasound department. Immediately attracted by the power of this visual medicine, he learned the basis in a radiology department in 1984. In 1985, at the time he took his first night responsibilities in critical care, radiologists were welcome in the ICU, but rather at opened hours for standardized examinations [3]. He took therefore, at these dark, pioneering times, the initiative of sometimes *borrowing* the ultrasound unit from the radiology department (desert after midnight), just trying to understand why this patient was unstable, with the deep feeling he was doing a duty to this patient.

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Since 1989, working at François Jardin's ICU, we had the opportunity to use the on-site ADR-4,000 at daylight [4, 5A]. This machine was, ironically, as large as the *laptops* machines (read below). At this time, our colleagues were not accustomed to the vision of physicians looking at free blood in trauma, inserting subclavian veins using ultrasound. This initiated a huge delay for the widespread of the tool. The challenge was to create a culture from two disciplines which had never been really familiar to each other: intensive care & radiology.

2.3 Having Adapted Echocardiography into a Simple, Holistic Model?

This field, initiated by pioneering names such as François Jardin, rapidly turned into a sophisticated domain, experts routes such as transesophageal one [6]. We have kept driving on the road of simplicity, developing a simple use, accessible to simple machines and steep learning curves, because these findings, associated to others (mainly lung ultrasound) proved to answer the clinical questions [5B]. Simple emergency cardiac sonography provides critical data using a simple machine with its microconvex probe. Visual approach to basic disorders is life-saving: detecting excessive fluid around the heart (pericardial *tamponade* usually), excessive right chambers volume (evoking pulmonary embolism), poor left ventricle contractility.

The label "simple cardiac sonography" (SCS) indicates that it is neither Echo (sophisticated echocardiography) nor ultrasound (traditionally evoking abdomen). It answers to a basic question apparently provocative: why do we want to see the heart? We found three settings: answering acute circulatory failure, acute respiratory failure, and cardiac arrest. The reader will see in the text that, each time the answer can be provided by looking at the direct disorder (obviously the lung in acute respiratory failure, sometimes the lung in cardiac arrest, in a more subtle way the lung in circulatory failure), the heart will appear as an interesting but indirect approach. In other words, the reader should ask, for understanding holistic ultrasound: before investing in sophisticated approaches, did we exploit *all* potentials of critical ultrasound? BLUE, FALLS, and SESAME protocols indicate in the next lines alternative pathways. Each time the cause is extracardiac (i.e., most cases), the cardiac approach can be simplified. Even some cardiac causes can be diagnosed using SCS. We must consider that some primary cardiac causes which should require sophisticated approaches (Doppler) and immediate surgical repair (mitral replacement e.g.) are not frequent, whereas circulatory failure from other causes are daily. In these rare cases, we are not opposed to ask for traditional approaches.

2.4 A Holistic Extension to the Whole Body?

The heart is only a beginning. In our dark nights, other critical targets were, for instance, abdominal bleeding and aortic aneurism rupture. Just these few conditions were so time-dependent that they justified the use of ultrasound by physicians in charge of such patients, instead of traditional systems, where the radiologist had to be called, an issue in nights or week-ends, but even at open hours, where each minute counted.

Many other targets were accessible in the abdomen: detecting bladder or kidney obstruction, analyzing inferior caval vein for volemia assessment, making safe tap on any suspect peritoneal effusion. Even pneumoperitoneum, a trouble usually not assessed using ultrasound, benefited from the rules applied to pneumothorax (read below) [7]. Mesenteric infarction benefited from dynamic (peristalsis) and static signs (portal gas), yielding high accuracy [8]. As to pancreas, biliary tract, etc., we still think they should be left in expert and accustomed hands for at least some time.

The head was a major target, if considering optic nerve as a marker of intracranial pressure [5C]. Bedside diagnosis of maxillary sinusitis decreased transportations to the CT.

The venous network is another familiar field with critical relevance for immediate diagnosis of *pulmonary embolism* (read BLUE-protocol). Regarding venous line insertion, as well as any procedure (puncture of abdominal or pleural fluid), we use our microconvex probe, and quite always the subclavian vein. We just consider that the label "vascular" probe is unsuitable. Linear probes fit to robots but not human beings, especially at the subclavian area, a point we were able to prove [9]. Since even the 1982 machine we used was suitable, we imagine the number of unnecessary troubles which occured during all these decades of blind punctures.

2.5 Lung Ultrasound?

Should an award be justified for having included the main vital organ in the armantarium of ultrasound?

During decades, ultrasound was applied in a standardized way, where the lung had no place [10]. How did we come to the opposite approach? Bringing into practice since 1985/1989 the potentials of critical ultrasound, feeling free to apply our probe on all areas without any preconception, the search for free blood, IVC and volemia, venous thrombosis, venous cannulation or optic nerve were basic targets [4], yet we saw as a priority to publish first all these findings regarding the lung.

For giving a chance to lung ultrasound to be a simple, accessible field, we propose a standardized approach. In the fast protocols developed by CEURF (BLUE-protocol, FALLS-protocol, SESAME-protocol, read below), three

standardized points (two anterior, one subposterior), called the BLUE-points are necessary and sufficient [11]. Ten signs allow to answer most concerns in the acutely ill. The bat sign indicates the pleural line, using rib shadows as a permanent landmark, highly useful in dyspneic, agitated patients. Arising from the pleural line, A-lines indicate air, a basic piece of information. Lung sliding indicates that this air is physiologic, i.e., alveolar. In M-mode, lung sliding generates the seashore sign. The quad sign is a unique sign for diagnosing all cases of pleural effusion, regardless echogenicity. The sinusoid sign indicates in addition that a small needle is suitable for withdrawing fluids. The fractal sign immediately indicates all cases of non translobar lung consolidation, i.e., alveolar syndrome, provided they are pleural based, i.e., most of them. The tissue-like sign is used for translobar consolidations. B-lines and lung rockets allow to diagnose interstitial syndrome, a new tool in the critically ill (see *BLUE-protocol, FALLS-protocol*). Abolished lung sliding and the A-line sign are two basic but nonspecific signs of pneumothorax. The lung point confidently rules in the diagnosis, i.e., the possibility to insert a chest tube on-site. With the dynamic air bronchogram (ruling out atelectasis) and the lung pulse (a sensitive sign of atelectasis), we reach twelve signs. Only the first ten are used in the BLUE-protocol, even less in the FALLS and SESAME protocols.

The LUCI-FLR project (Lung Ultrasound in the Critically Ill Favoring Limitation of Radiographies) is one application which does not aim at eradicating X-rays (the idea, as well as the resulting acronym, would be scary). More reasonably, it aims at making 30 % less radiographs and 70 % less CTs in critically ill patients in the next 30 years. For the 5 main applications (normal lung surface, pleural effusion, alveolar syndrome, interstitial syndrome, *pneumothorax*), ultrasound is nearly as accurate as CT, ranging from 90 to 100 %. In some fields, ultrasound is superior: higher resolution, enabling to detect necrosis within consolidation [12], septations within pleural effusion, all dynamic data (lung sliding, air bronchograms, diaphragm...). Mingling this slight inferiority with its slight superiority, it is possible to consider ultrasound as a reasonable, bedside, gold standard.

Many other applications include managing ARDS (the Pink protocol), pregnant women, obese patients, trauma patients, who all can benefit from the *same* approach. The signs are the same in neonates [13]. Thoracentesis is made safe [14]. Some targets seem to be recently of interest to intensivists (diaphragm recognition, alveolar recruitment) although we develop little space for them.

2.6 A Definition of Holistic Ultrasound?

What is *holistic ultrasound* by the way? It can simply be defined as a field where each element interacts with all others. It regards the machine, the probe, the applications. It uses simplicity, includes the whole body, accessible with one universal probe. Reading our 320 pages latest textbook [15] would be exhausting, and just some charicatural examples will be given.

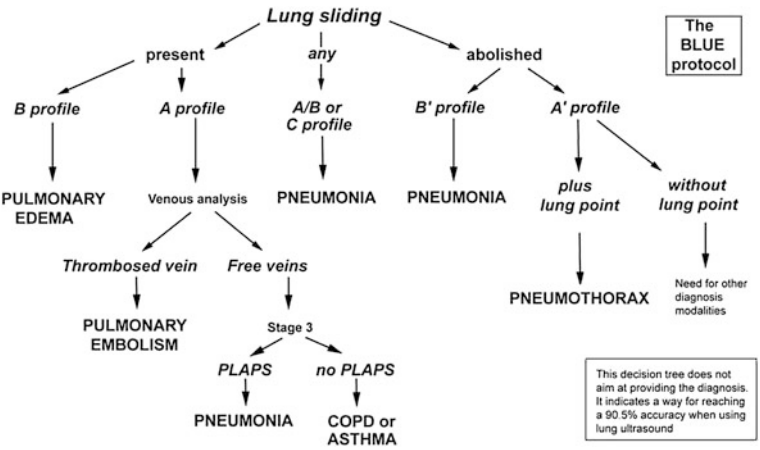

Fig. 2.1 The decision tree of the BLUE-protocol

Example 1: the BLUE-protocol makes echocardiography a simpler discipline

Echocardiography, an expert field reserved to an elite, is often used for *acute respiratory failure*. By assessing the lung, BLUE-protocol makes a different but *direct* approach. The BLUE-protocol is designed to diagnose hemodynamic pulmonary edema (HPE), pneumonia, pulmonary embolism, pneumothorax, COPD & asthma with an overall 90.5 % accuracy (Fig. 1). For example, HPE generates quite always lung rockets disseminated at the anterior chest wall and associated with lung sliding, the whole being called the B-profile. Less than 30 s are usually necessary. During this fast protocol, diagnoses are ruled out: pneumothorax (definetely), COPD and asthma (quite definitely), and pulmonary embolism (unlikely since a normal anterior lung surface is expected here). The diagnosis of pneumonia is a little more subtle, since 4 profiles can be seen (see Fig. 1). In the native article, pneumonia included cases of ARDS, and these profiles are able to distinguish ARDS from HPE in most (86 %) cases. The heart is not included in the BLUE-protocol but associated. Lung plus simple heart make the same (if not better) than traditional Doppler-echocardiography. For instance, assessing for diastolic LV dysfunction makes less sense if there is no sign of pulmonary edema. This approach, found again in FALLS-protocol, can be of major interest for young intensivists who have not yet completed traditional echocardiographic trainings, each time, in spite of an achieved culture, cardiac windows are lacking, each time TEE is not immediately available, not yet bought, or impossible to buy, i.e., most settings in the world.

Many questions regarding the BLUE-protocol, answered in [15], deal with the case of pulmonary embolism without DVT, why lung infarctions are not taken into account in the diagnosis of pulmonary embolism, how can one do with traditional laptop machines and traditional probes, how about rare ou double diagnoses, what

are the expectations of the BLUE-protocol when developed in poor countries, a.m.o.

Example 2: Cardiac arrest.

SESAME-protocol is devoted to extreme circulatory failure and *cardiac arrest*. Unlike some protocols, SESAME-protocol begins with the lung. This provides, in (far) less than three seconds per lung, a confident answer since there is always a lung window (as opposed to heart). In the case of A′-profile, pneumothorax is immediately suspected. In the case of A-profile, major hypovolemia as a cause can be envisaged, and fluid therapy can be given in parallel to resuscitations. Then a cardiac analysis follows (tamponade is a main diagnosis). In this specific setting, where every second matters, a really small machine (30 cm width), allowing optimized speed for on-site transportation, switching on in 7 s is a legitimate requirement. SESAME-protocol uses only one probe, a major advantage when one considers that many reversible causes of cardiac arrest—mainly in trauma—come from hemopericardium (usually requiring cardiac probe), tension pneumothorax (linear probe), or abdominal bleeding (abdominal probe). Holistic ultrasound is used again because the same probe allows detection of one lung intubation and central venous line placement.

Example 3: the top of the machine: why is it useful

Laptops have no top. Therefore, probes, gel, etc., lay on lateral stands, increasing again difficulty to move them through tiny environments (ICU, OR., ER). On a machine with a top, probes can be fixed on it. The philosophy of the unique probe allows precisely to exploit the small size ot the top (29 cm width). Not only the choice of the unique probe allows fast protocols (SESAME), but in addition makes the machine slimmer.

2.7 The Description of a Possibly Direct Parameter of Clinical Volemia?

The FALLS-protocol is another example of holistic ultrasound. With the same tool, our universal microconvex probe, and the use of simple cardiac sonography, the cause of *acute circulatory failure* will be assessed sequentially, following Weil's terminology [16]. One just has to think different (Fig. 2.2). A simple cardiac sonography with some BLUE-protocol excludes rapidly an obstructive shock: tamponade, right heart dilatation, tension pneumothorax. DVT is seen in 81 % of cases of pulmonary embolism, making the diagnosis quite confident [17]. Then BLUE-protocol rules out cardiogenic shock (left, i.e., most causes) in the absence of a B-profile. The A-profile (or equivalents: A/B, C profile), usually present, indicates a clearance for fluid therapy in such patients, called FALLS-responders: they have either hypovolemic or distributive shock. Patient's improvement with no change of the A-profile indicates *hypovolemic shock*. Absence of improvement (clinical, biological) under fluid therapy, with an A-profile changing to a B-profile (defining the FALLS-endpoint), rules out the diagnosis of hypovolemic shock.

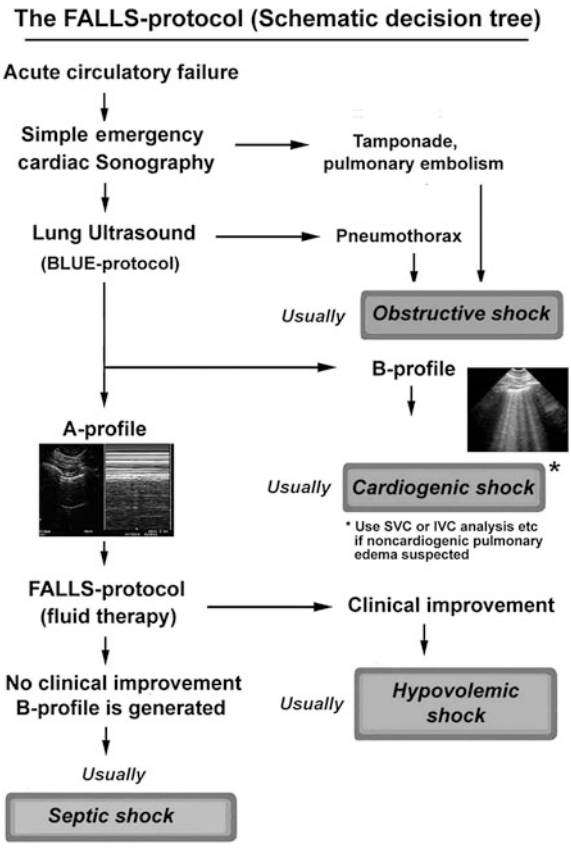

Fig. 2.2 FALLS-protocol, decision tree. The A-profile is featured, combining anteriorly A-lines with lung sliding. The B-profile associates lung rockets (here featuring) and lung sliding. This decision tree is schematical, and includes the most frequent causes. Note that some rare causes, such as cardiogenic shock seen in right ventricle infarction, a cardiogenic shock not associated with elevated wedge pressure, do not contra-indicate the use of FALLS-protocol, where here a fluid therapy would be undertaken. Many other precisions are useful for wise use of the FALLS-protocol

This occurs at a PAOP of 18 mm Hg [18]. The only remaining mechanism is distributive shock, i.e., mainly, *septic shock* (anaphylactic shock is usually an easy diagnosis, which also requires fluid therapy, the rare spinal shock occurs in suggestive settings).

At this step, holistic ultrasound was used, i.e., a same probe for heart, lungs and veins, and a simplified use of echocardiography, combined with lungs and veins. FALLS-protocol can be associated with no drawback, time permitting, with any of the traditional tools (Swan-Ganz catheter, echocardiography, PICCO, etc.).

FALLS-protocol suggests that the change from A-lines to B-lines during fluid therapy can be considered as a direct marker of clinical volemia, occurring at an early step of pulmonary edema. In addition, this step is infraclinical [19]. We are fully aware of the challenges raised by sepsis [20], and remain open to any criticism. The answers to many questions are available in [15]. How about PAOP as a reference? How about right heart dysfunction? Are patients with septic shock plus ARDS a limitation? Can patients be managed without knowledge of the cardiac index? We just answer, shortly, to this last one: these patient actually can, since

FALLS-protocol identifies which ones can benefit from fluid, and when should fluid be stopped.

2.8 An Early Training Center for Widespreading Critical Ultrasound?

Numerous training centres are, now and fortunately, widely available. They provide quality training. It would be very difficult in 2013 to make a comprehensive list of the actors who contribute to widespread ultrasound for the clinician, it would be endless and we quote some milestones [21–24]. In the institution where we were working, a training fully adapted to the critically ill was available since 1989. Twenty four years later, CEURF still widespreads this holistic vision.

2.9 Maybe for Having Always Favored Simple Systems

We are glad to use, since 1992, a Japanese machine of perfect size, and which has all features we require. Even the 1982 technology we used before had respectable performances.

Our 1992 machine is the fastest ever built with 7 s of start-up time, the cleanest with its flat keyboard, and one of the simplest when one cares at mechanically hiding most buttons for keeping the 4 necessary ones. Its resolution can be appreciated in [15]. Ironically, this machine is one of the smallest with 30 cm width. The width is the only interesting dimension, because the height is not a limiting factor in hospital use (ceilings are high enough). The wheel, an ancient but smart technique, is in actual fact the main factor allowing bed to bed use. With our Hitachi 405, it was useless to wait for the laptop revolution (which made good machines).

The *microconvex probe* we use has the advantage, to our opinion, to be universal. It analyzes from 1 to 17 cm. Its small footprint allows assessment of quite all areas, from large (abdomen) to tiny ones (intercostal space, subclavian area...). Quite all images of our textbooks, from 1992 to 2011, were taken using it. Using one probe has the advantage of cost, speed, and a better control of infection: in an urgent examination, for each change of probe, time lacks for cleaning probe and environment. We do not use Doppler, a credible alternative when considering that holistic ultrasound adds lung to heart, which deeply simplifies the cardiac analysis.

2.10 Maybe also for Having Suppressed Gel

Gel is a traditional part of ultrasound, making it a rather *gooey* discipline. CEURF has conceived a product which spontaneously vanishes without any disturbance to the patient. It allows major time saving (from one area to another, less than 2 s are

used). It solves one problem of echocardiography during cardiac arrest: gel makes landscape slippery. No need to wipe *Echolite* since its viscosity is designed for not interfering with the resuscitation maneuver.

This is one (not so) futile example of holistic ultrasound. Such a change does certainly not deserve an award, but we must admit it changed *our* daily life.

2.11 Conclusions

Critical ultrasound is a holistic discipline. We saw some examples through the text. Yet the term "holistic" means something more: ultrasound can travel out of the narrow rails of critical care, and the same rules can be used *with no adaptation,* in many less critical disciplines, especially regarding the lung [25]. Basic cardiology, pulmonology, pediatrics, thoracic surgery, internal medicine, etc., can take advantage of it. Ultrasound is a window for a *visual medicine*, aiming at making a more simple medicine, more efficient. Including vital organs such as the lung make it really holistic. An award prize at the APICE congress for this? Probably not, although such an award should have been given at the birth of ultrasound (1950s), to its creators, since this technique has never been really recognized. In actual fact, more than a tool, critical ultrasound may be considered as a philosophy, of major interest to the patient, and maybe as the beginning of a new discipline.

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Assessment and Management of Circulatory Failure

3

Kamen Valchanov

3.1 Introduction

Heart failure (HF) is a growing healthcare problem. HF affects almost 1 million people in the UK and 60,000 new cases are diagnosed each year [1]. It has an overall population prevalence of up to 3 %, rising to 10 % in the very elderly. With the growing overall age of the population in the developed countries as well as advances in medical care allowing patients with co-morbidities to live longer, it is likely the prevalence of HF will increase in the future, and the demand for advanced treatment to grow.

Most heart HF are diagnosed and managed as outpatients. Following a first hospital admission for HF, patients have a 5 year mortality of 75 %, which is worse than that for many forms of cancer [2]. However, as there is no effective cure of the condition many go through its natural progression and 5 % of congestive heart failure patients develop advanced congestive heart failure (ACHF) [3]. Most patients admitted to hospital with ACHF suffer acute decompensation of chronic disease but some patients with new onset HF present in extremis. Patients with impaired ventricular function who undergo surgery may present with low output states in the intensive care units (ICU).

HF patients are admitted to ICU for fluid management, inotropic support, mechanical support, haemofiltration, perioperatively, and following cardiac arrest. In addition many patients admitted in ICU for another reason suffer from HF pathophysiology. The typical ACHF patient is admitted to ICU in the context of acute decompensated heart failure and is most commonly older than 70 years of

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age, has a history of HF, coronary artery disease and hypertension. There are an equal number of men and women.

Life expectancy after diagnosis of HF has been improving over the years [4] but the in-hospital mortality is as high as 4−7 % [5]. For the survivors, the risk of subsequent hospital readmission is high.

Clinicians must now also consider the increasing number of young adults with grown up congenital heart disease (GUCH) developing ACHF needing intensive care [6].

3.2 Definitions

HF is a complex clinical syndrome characterized by dyspnoea, fatigue, limited effort tolerance and fluid retention. The European Society of Cardiology and the American College of Cardiology/American Heart Association [7] define advanced HF as a clinical syndrome manifested by the presence of the following symptoms despite optimal therapy: (1) dyspnoea of NYHA class III or IV, (2) episodes of fluid retention, (3) severely impaired functional capacity (6 min walk less than 300 m, peak O2 consumption less than 12−14 ml/kg/m^2), objective evidence of severe cardiac dysfunction (left ventricular ejection fraction less than 30 %), pseudo-normal or restrictive left ventricular filling pattern on Doppler studies, pulmonary wedge capillary pressure greater than 16 mm Hg (or right atrial pressure greater than 12 mm Hg), hospitalisations related to HF (more than 1 in the past 6 months) and elevated blood levels of natriuretic peptides.

3.3 Pathophysiology

A unifying hypothesis to satisfactorily explain the clinical syndrome of HF has proved impossible. A deeper understanding of the pathophysiology of HF, has led to the development of more complex models and, as a result, the evolution of new treatment strategies. The cardio-renal model proposed that sodium and water retention was caused by abnormal renal blood flow. The cardio-circulatory model proposed that low cardiac output and peripheral vasoconstriction were the primary problem. The neuro-humoral model attempted to explain the syndrome as a prolonged and pathological activation of several homeostatic and compensatory mechanisms in response to end organ damage. Recently, immunological and genetic factors have been shown to affect susceptibility and severity. Ventricular remodelling and endothelial dysfunction are also features of this syndrome [8].

3.4 Diagnosis

3.4.1 History and Examination

Most of the diagnoses in medicine can be achieved by clinical history and examination. 77 % of HF diagnoses can be achieved by history taking alone [9]. Added to this simple examination of the neck and diagnosis of elevated central venous pressure (CVP) can increase the diagnostic yield further [10]. Other cardinal signs like tachycardia, diminished pulse pressure, pulsus alternans, S3 gallop, increased heart border, auscultatory signs of pulmonary oedema can derive the diagnosis in almost all patients.

3.4.2 Clinical Features

Patients with ACHF most commonly present with features of volume overload and poor organ perfusion as manifested by cool extremities. Those patients requiring ICU usually have one of two clinical syndromes: Pulmonary oedema, accompanied by severe respiratory distress and low oxygen saturation; or cardiogenic shock, defined as tissue hypoperfusion induced by HF after correction of preload. It is usually characterized by hypotension (systolic BP < 90 mm Hg), oliguria (<0.5 ml kg^{-1} h^{-1}) and evidence of organ dysfunction. As a result of poor pump function and peripheral hypoperfusion, there are a number of co-morbidities, which may be present on admission or develop later complicating management. These include renal and hepatic dysfunction, respiratory failure, sepsis, and cognitive impairment.

3.4.3 Investigations

In addition to a detailed history and clinical examination, a number of investigations are required in hospitalised patients:

Electrocardiogram (ECG) to determine rhythm and aetiology of HF (acute coronary syndrome, myocarditis);

Chest radiograph (CXR) for heart size, pulmonary congestion, lung consolidation, pleural effusions;

Echocardiography to evaluate and monitor regional and global ventricular function, valve structure and function, pericardial effusion, and mechanical complications of myocardial infarction. The pulmonary artery systolic pressure may also be estimated from the tricuspid regurgitation jet;

Blood tests: Full blood count, coagulation screen, C-reactive protein, creatinine and electrolytes, glucose, liver function tests in all patients. Troponin and brain natriuretic peptide (BNP) levels may assist in confirming the diagnosis and allow an estimation of severity;

Coronary angiography, to determine if revascularisation should be contemplated;

Cardiac CT and MRI provide additional morphological data in HF patients but are often not practical for patients needing admission to ICU.

3.4.4 Monitoring

Non-invasive monitoring: Temperature, respiratory rate, blood pressure, continuous ECG, and pulse oximetry are required in all patients;

Invasive blood pressure: In unstable patients continuous arterial blood pressure monitoring and repeated blood gas analysis is essential;

CVP: Monitoring right sided filling pressure is essential in patients with ACHF and a central venous catheter is useful for the delivery of vasoactive medication. Estimation of central venous or right atrial oxygen saturation can be an important marker of oxygen utilisation;

Pulmonary artery catheterisation (PAC): In patients with left ventricular dysfunction, right atrial pressure does not correlate well with left sided filling pressure; therefore, an estimate of left atrial pressure is valuable. In patients requiring inotropic or vasoconstrictor drugs, monitoring of cardiac output (CO) and estimation of systemic vascular resistance facilitates rational therapy based on pathophysiological principles. Whilst PAC is the "gold standard" [11], there are many other less invasive modalities on the market, which can derive these measurements. Mixed venous oxygen saturation can also be monitored with a PAC and is particularly useful in the presence of severe tricuspid regurgitation, which can cause difficulties with direct measurement of cardiac output. In patients with high pulmonary vascular resistance (PVR) associated with heart failure direct measurement of pulmonary pressures is important.

Transoesophageal echocardiography (TOE) has recently gained popularity as a haemodynamic monitoring tool for ventilated intensive care patients. It provides valuable information about morphology and haemodynamic state but interpretation of data requires considerable training and experience. Transthoracic echocardiography is also commonly performed, and is well established.

3.5 Treatment

The widened range of therapeutic options in heart failure has, paradoxically, made clinical decision-making more difficult. Nevertheless, the aims of management can be simply stated:

Preventative—the identification and treatment of conditions associated with the development of HF;

Symptomatic—interventions to reduce dyspnoea, fatigue, peripheral oedema and end-organ dysfunction, and improve effort tolerance;

Prognostic—interventions to slow, halt or reverse disease progression; reduce the frequency of hospital admissions and increase life expectancy.

Treatment strategies for ACHF patients in ICU should be based on the underlying pathophysiology, aiming to reverse the haemodynamic abnormalities detected [12] (Fig. 3.1). Where an underlying treatable cause is identified, the clinical condition must be optimised so that definitive treatment can be carried out with the minimum of risk. Immediate therapy should focus on the patient's symptoms, and reducing congestion is often the most effective way of achieving this. Treatment strategies can be divided into clinical and haemodynamic.

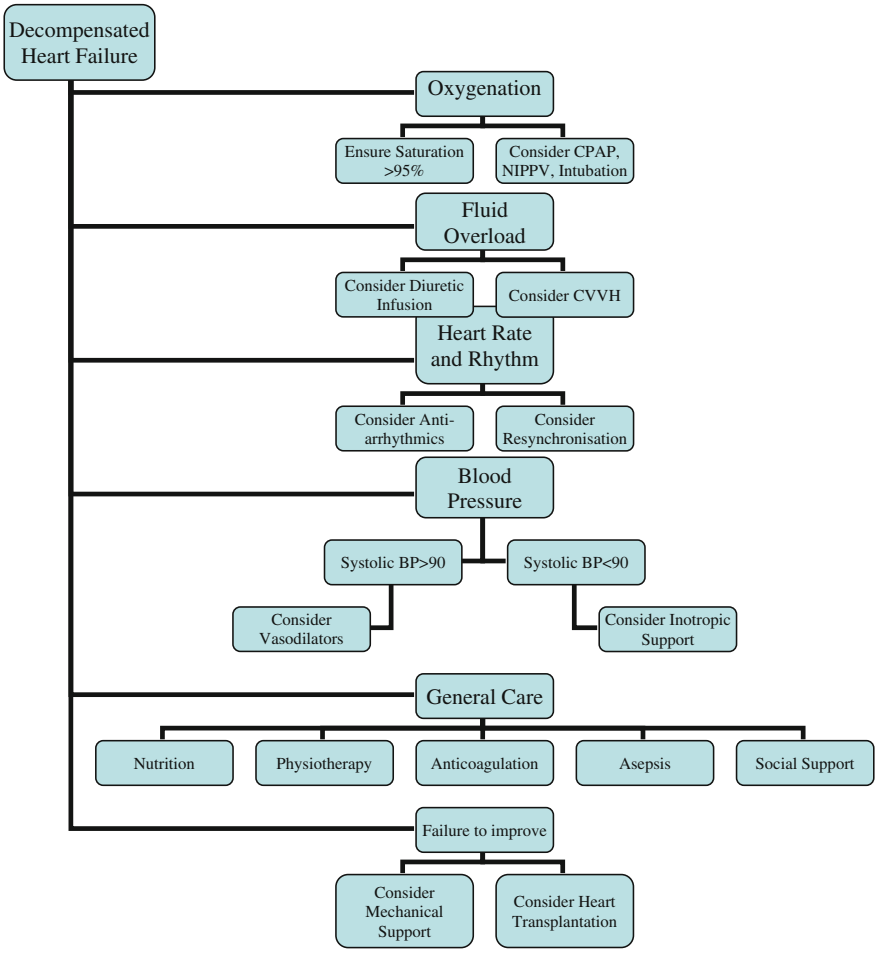

Fig. 3.1 Treatment strategies for management of heart failure in ICU [12]

3.5.1 Clinical

1. Elimination of peripheral and pulmonary oedema
2. Systolic blood pressure above 90 mm Hg
3. Stable or improving renal function
4. Improving or normal liver function and coagulation parameters
5. Adequate oxygenation.

3.5.2 Haemodynamic

1. Central venous/Right atrial pressure <8 mm Hg
2. Pulmonary capillary wedge pressure <16 mm Hg
3. Cardiac index >2 l/min/m2
4. Mixed venous oxygen saturation >60 %
5. A secondary goal is systemic vascular resistance 800−1,200 dynes/s/cm5.

3.5.3 Oxygenation

Adequate level of oxygenation at the cellular level is essential to prevent end-organ dysfunction. Respiratory muscle fatigue often results from hypoxaemia and low CO. Continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) can be used to reduce the work of breathing. When NIPPV does not correct hypoxia, or there is reduced level of consciousness, invasive mechanical ventilation is indicated.

3.5.4 Haemodynamic Support

Medical therapy consists of reducing venous congestion (optimal preload), optimising afterload, inotropic support, and anticoagulation.

1. Reducing venous congestion
   The reduction of elevated filling pressures is the most effective way to relieve symptoms of HF. Loop diuretics: Bolus doses and infusions of furosemide have both been used [13]. A very large bolus of diuretic may also lead to reflex renal vasoconstriction and a higher risk of ototoxicity. Fluid restriction is an important adjunct to diuretic therapy in severely fluid overloaded patients. Using a fluid challenge in volume-overloaded patients with obvious peripheral oedema is counterproductive; inadequate urine output in these patients is invariably related to a low cardiac output and treating this often requires inotropic therapy. Thiazides: The combination of a thiazide with a loop diuretic increases the urine volume significantly in patients with ACHF. Aldosterone antagonists: Once diuresis is induced it is important to monitor serum

potassium, as hypokalaemia is associated with arrhythmias. Combining loop diuretics with an aldosterone antagonist like spironolactone helps maintain adequate serum K^+.

2. Optimising afterload
   Vasodilators: In the absence of severe hypotension, vasodilators are indicated in most patients with acute heart failure [14]. Decreasing preload relieves congestion and decreasing afterload increases cardiac output as most patients with HF are vasoconstricted. When administering vasodilators and/or positive inotropic drugs the following equation is useful in manipulating the circulation: MAP – CVP = CO × SVR (mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), systemic vascular resistance (SVR)).
   Nitrates: In low doses, nitrates are venodilators but high doses cause arterial dilatation as well. They are particularly useful in acute coronary syndromes associated with heart failure. Recombinant BNP (nesiritide) relaxes smooth muscle leading to arterial and venous dilatation. It leads to an increase in cardiac output without direct positive inotropic effect. Compared to nitroglycerin, nesiritide produces faster relief of dyspnoea and a more pronounced decrease in pulmonary capillary wedge pressure. There is no conclusive evidence that nesiritide improves renal function and a meta-analysis [15] showed that it may actually worsen renal failure. Clinical studies have not confirmed improved outcomes and at present the role of nesiritide in the management of heart failure remains unclear. Hydralazine: A combination of hydralazine and nitrates has been shown to be beneficial in patients with chronic HF.
3. Inotropic agents
   Inotropic agents are indicated in the presence of tissue hypoperfusion and pump failure, often manifested by worsening renal function or fluid retention refractory to treatment with diuretics and vasodilators. In these patients it is essential to improve the patient's haemodynamic state, however, it must be remembered that positive inotropic agents demonstrate short-term beneficial haemodynamic effects but increase myocardial oxygen consumption and accelerate underlying disease progression. There is also a risk of inducing life-threatening arrhythmias. Rational use of inotropic therapy in ICU requires invasive haemodynamic monitoring.
   Adrenergic agonists: Despite the desensitisation of β-receptor pathways in the failing human heart, most patients with advanced heart failure still show a response to adrenergic agents.
   Dopamine: Lower doses (<2 mcg kg^{-1} min^{-1}) are thought to act predominantly on peripheral dopaminergic receptors leading to vasodilatation. An increase in renal blood flow may lead to diuresis. Higher doses (>5 μg kg^{-1} min^{-1}) increase cardiac output and have α-adrenergic effects increasing peripheral vascular resistance and blood pressure.
   Dobutamine: It stimulates $\beta 1$ and $\beta 2$ receptors and is positively inotropic and chronotropic. There may be a secondary decrease in sympathetic tone

decreasing PVR. At low doses it may also induce mild arterial vasodilatation. High doses of dobutamine (>10 μg kg^{-1} min^{-1}) cause vasoconstriction but the effect varies between patients.

Epinephrine: It has a high affinity for β1, β2 and $\acute{\alpha}$-receptors producing inotropy, chronotropy, dromotropy and splanchnic hypoperfusion.

Norepinephrine: It increases SVR because of its affinity for $\acute{\alpha}$1-receptors. The lowest dose required to increase the SVR, and to maintain perfusion of vital organs should be used.

Phosphodiesterase inhibitors: Type III PDEIs inhibit the breakdown of cAMP. Enoximone and milrinone are the two agents used in clinical practice and both cause marked peripheral vasodilatation whilst being positively inotropic. They are therefore useful in patients with advanced heart failure who have an elevated SVR but are still hypotensive because of a very low cardiac output.

Levosimendan: It has two main mechanisms of action: Ca^{2+} sensitization of the contractile proteins (positive inotropic effect) and smooth muscle K^+ channel opening (peripheral vasodilating effect). Intravenous infusions of levosimendan are usually maintained for 24 h, but the haemodynamic effects persist because of the long half-life of its metabolite. Levosimendan infusions in patients with heart failure have been associated with a dose-dependent increase in stroke volume and CO, decline in the pulmonary capillary wedge pressure, decrease in SVR and PVR, slight decrease in blood pressure and a slight increase in heart rate.

4. Anticoagulation

   In acute coronary syndromes and in atrial fibrillation, the role of anticoagulation is well established. Patients with a history of an embolic event or evidence of intracardiac thrombi should also receive anticoagulation. Pulmonary emboli are also commonly associated with ACHF and it is reasonable to anticoagulate bed bound critically ill patients. Care is needed as concomitant liver dysfunction may lead to a prolonged prothrombin time.

5. Ultrafiltration

   Patients with gross fluid retention and hyponatraemia, further aggravated by diuretics, present a difficult clinical problem. Inotropic drugs may improve renal perfusion and increase urine output. If this is unsuccessful continuous veno-venous haemofiltration should be considered. This is very effective in removing fluid and the rate of fluid removal can be tailored to the patients' needs. If necessary, large volumes of fluid can be removed in a relatively short time to get the patient ready for a definitive procedure (heart transplantation, mechanical circulatory support).

6. Resynchronisation therapy

   Patients with heart failure often manifest intra and interventricular dyssynchrony (usually associated with a wide QRS complex on the surface ECG), which contributes to the low CO. Resynchronization with bi-ventricular pacing increases cardiac output, reduces mitral regurgitation, and improves survival as well as quality of life.

When medical therapy fails to control the haemodynamics of ACHF patients, heart transplantation or mechanical circulatory support should be considered.

3.6 Cardiac Transplantation

Replacing the damaged heart by a new one, i.e. cardiac transplantation is a possibility for some patients. The mismatch between demand and availability of organs, the physiological conditions at presentation, and the waiting time, makes this option unrealistic for many patients. Mechanical support is an immediate solution that can be used as a bridge to transplantation (with a few patients recovering while waiting). In some circumstances, the mechanical support may be the only treatment offered (destination therapy). Other methods of promoting myocardial recovery (gene therapy, stem cell therapy) may also be used in the future on a platform of mechanical support.

3.7 Mechanical Cardiovascular Support

Mechanical circulatory support can be classified based on:

The duration of support that can be provided: short or long term;
The flow characteristics of the pump: pulsatile or continuous flow;
The ventricle supported: right/left/biventricular support;
The pump driving mechanism: pneumatic/electrical.

Numerous modalities of mechanical support are on the market in 2013. For the purposes of this article only Intra-aortic balloon conterpulsation, extracorporeal membrane oxygenation, short-term ventricular assist devices and percutaneous continuous flow systems will be discussed due to their importance in ICU.

3.7.1 Intra-Aortic Balloon Counterpulsation

The intra-aortic balloon pump (IABP) was developed in the early 1960s (Fig. 3.2) [16]. It improves the ratio between oxygen demand and supply in the myocardium, by causing systolic unloading and diastolic coronary blood flow augmentation. As a consequence, there is an increase in CO, coronary perfusion, renal, and splanchnic blood flow with a concomitant decrease in left ventricular wall stress, SVR, and pulmonary capillary wedge pressure. The IABP is commonly used in the management of cardiogenic shock, principally when recovering from cardiac surgery or acute myocardial infarction. Early use in ACHF has been reported as advantageous [17] and leading to better outcomes [18, 19]. The evidence to support this practice has not yet been acquired, and in fact a large randomised controlled trial of IABP in acute cardiogenic shock failed to demonstrate any survival benefit [20].

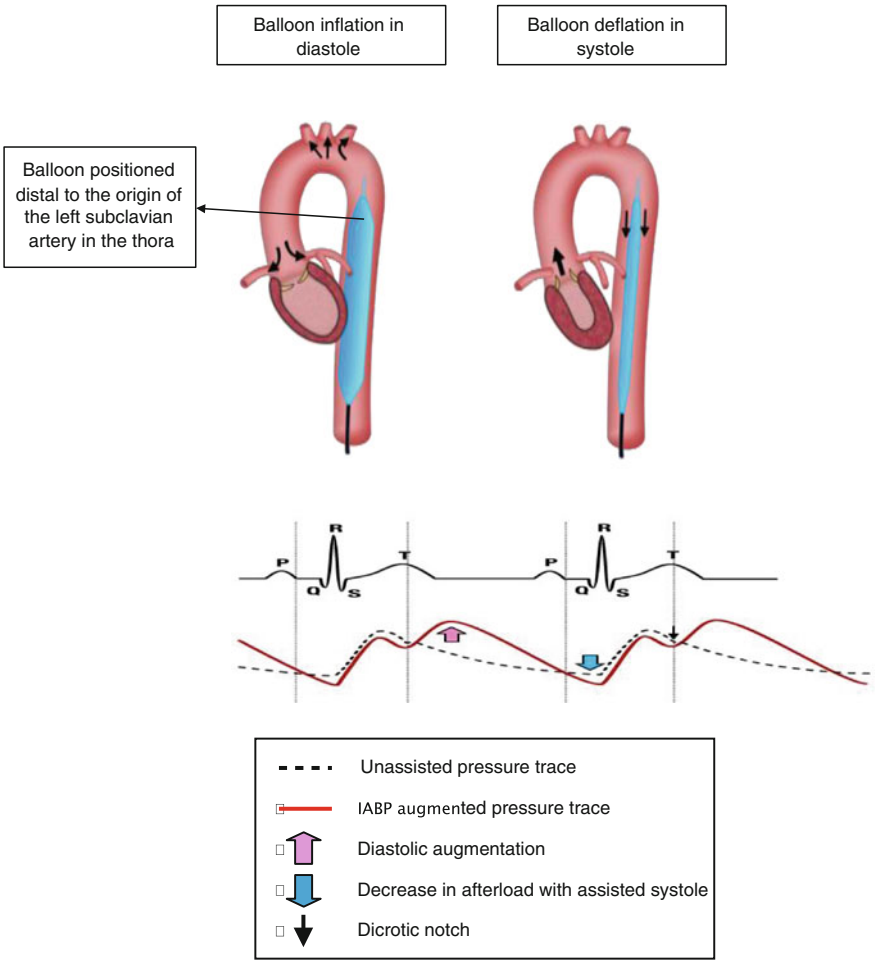

Fig. 3.2 Intra aortic balloon pump (IABP) [16] is inserted into the descending aorta and its balloon is inflated with helium during diastole, then rapidly deflated during systole. The *first diagram* shows inflation of the balloon in diastole, causing diastolic pressure augmentation resulting in improved coronary perfusion. The *second diagram* shows deflation in systole, causing decreased afterload. The triggers for inflation and deflation of the balloon are preferably derived from the ECG but can also be derived from the arterial pressure trace

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3.7.2 Extracorporeal Membrane Oxygenator (ECMO)

Veno-arterial ECMO has been successfully used in the paediatric heart failure population for a long time. Its use in adult patients is increasing in recent years. It offers temporary support until recovery, or until a decision is made between the options of longer-term mechanical support or cardiac transplantation. ECMO is an adaptation of cardiopulmonary bypass technology and can be central (using intrathoracic cannulation sites) or peripheral (usually using percutaneous approach to cannulate the femoral vessels) (Fig. 3.3). It functions as an artificial heart and lung by providing non-pulsatile blood flow through an external circuit and an interface for oxygen and carbon dioxide exchange [21].

Peripheral VA ECMO is less invasive and can be instituted at the bedside. However, it may not adequately decompress the left ventricle. Limb ischemia distal to the cannulated femoral artery is a potential complication especially when support is continued for prolonged periods.

Central VA ECMO offers excellent flows and better left-ventricular decompression. It necessitates chest opening and is associated with higher bleeding and infective risks. It is always carried out by a cardiac surgeon I an operating theatre.

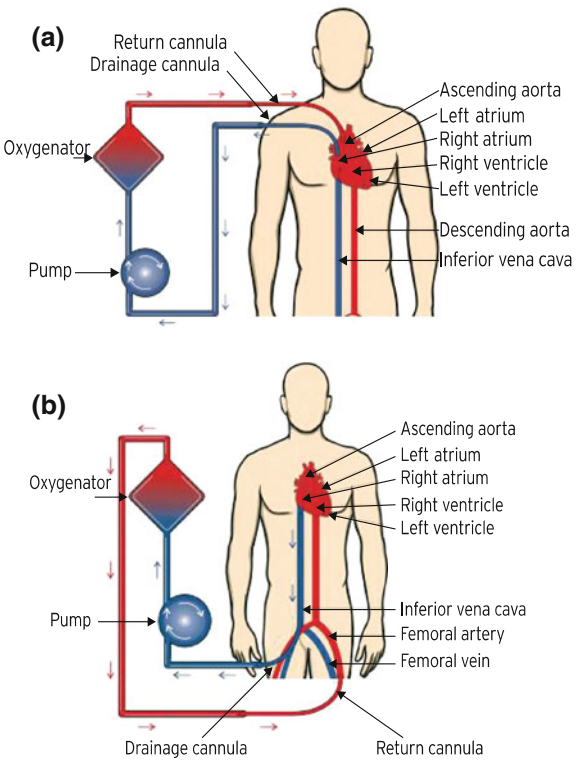

Fig. 3.3 Cardiac ECMO Hung et al. [21] **a** Central VA ECMO: Blood is pumped from venae cavae or right atrium through oxygenator and returned into the ascending aorta. **b** Peripheral VA ECMO: Blood is pumped from right atrium/inferior vena cava through oxygenator and returned into a femoral artery

3.7.3 Short Term Ventricular Assist Devices

These are continuous-flow devices (Centrimag [16], Fig. 3.4, as an example) used successfully for short-term cardiovascular support. The major difference between these devices and ECMO is that they former lack an oxygenator, i.e. the patient's respiratory function must be adequate. The internal impeller is electromagnetically levitated and centred, eliminating the need for shafts, seals, and bearings in the pump causing little haemolysis, thrombus and particle formation [22]. These are simple uni- or bi ventricular support devices. The blood is drained from the patient through centrally placed venous cannula in the right or left atrium, and blood returned to the patient through centrally placed arterial cannula in the pulmonary artery or ascending aorta.

3.7.4 Percutaneous Continuous Flow systems

To avoid the need for sternotomy exclusively percutaneous continuous flow systems have been developed. The most commonly used ones are Tandem Heart pump and the Impella.

The Tandem Heart [16] (Fig. 3.5) provides the circulating power to pull oxygenated blood from the left atrium and to return it to the systemic arterial circulation. It requires percutaneous placement of a cannula in the left atrium accessed via the femoral vein and a trans-septal puncture. A femoral arterial cannula is placed for systemic return. It can achieve up to 4 l/m of continuous flow with the aid of an externally placed pump. The trans-septal puncture can be difficult and requires fluoroscopy or TOE [23]. Complications of trans-septal puncture include cardiac perforation and tamponade.

Impella [16] (Fig. 3.6) is a percutaneously placed partial circulatory assist device. It is a non-pulsatile micro axial continuous flow blood pump that spans

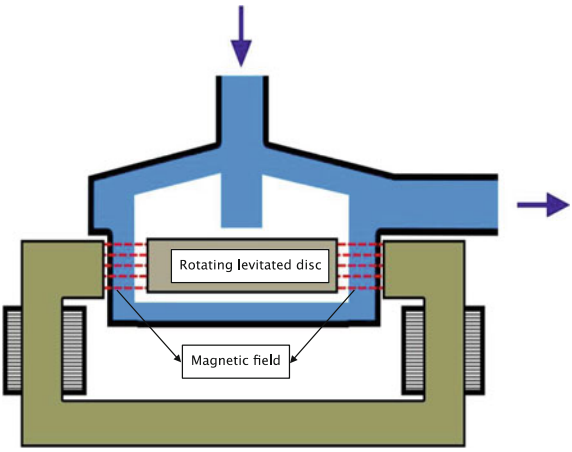

Fig. 3.4 Centrimag pump head [16]. The figure shows a *magnetic disc* levitated in a *magnetic field*, which due to its rotations imparts kinetic energy to the blood flow coming into the chamber

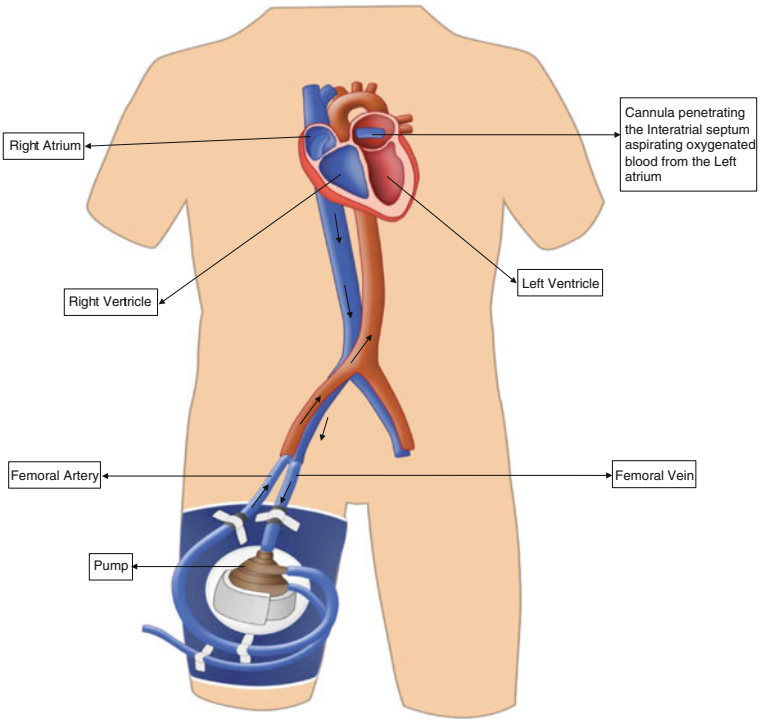

Fig. 3.5 Tandem heart. It requires trans-septal puncture and drainage line aspirating blood from the left atrium and being returned into the femoral artery [16]

through the aortic valve. It has been advocated for temporary support during high-risk percutaneous interventions. It aspirates blood from the left ventricle and displaces it into the ascending aorta, rapidly unloading the left ventricle and increasing forward flow.

3.7.5 Long Term Ventricular Assist Devices

Patients who are not expected to recover from ACHF or receive heart transplantation soon may need long-term ventricular assist devices. In some cases these are used for preoptimisation of patients for heart transplantation over months or years. These devices can be used to support left, right, or both ventricles. Whilst early systems utilised pulsatile flow, and were mostly pneumatic volume displacement pumps, the modern devices are non-pulsatile and lack some of the problems associated with the early devices. The modern systems have simplified design with only a single moving part, better long-term reliability, thromboembolism is less frequent, and quality of life is significantly better than with pulsatile devices.

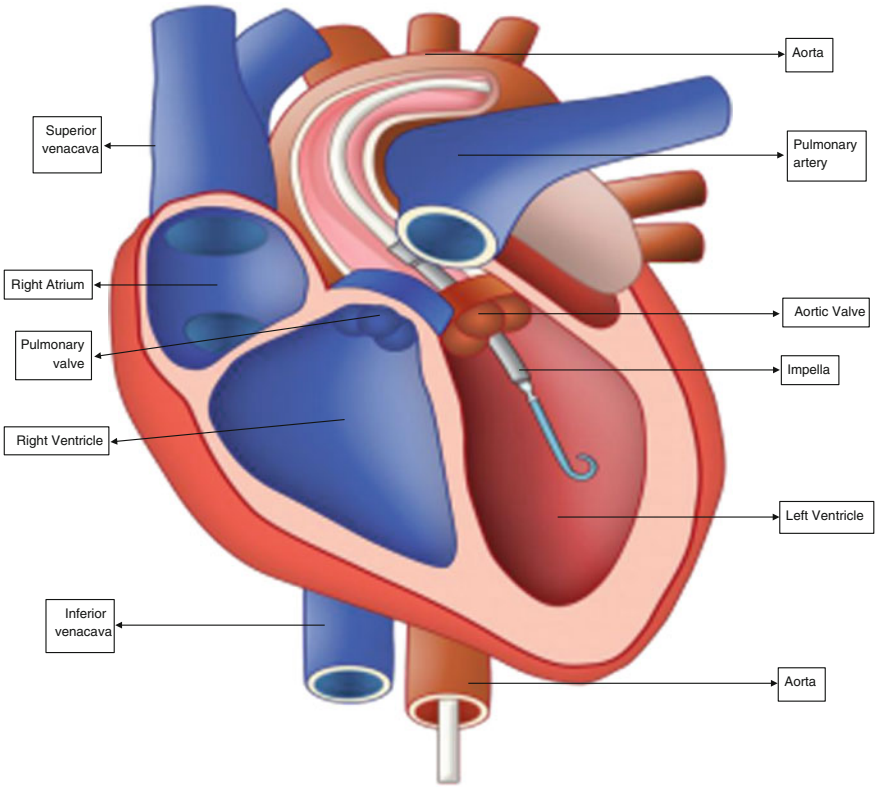

Fig. 3.6 Impella. Spinning micro axial pump propels blood across the aortic valve [16]

Total artificial heart: The SynCardia total artificial heart [24] is a pulsatile alternative to biventricular devices in the bridge to transplant setting. It is only suitable for a limited population because of its size.

3.8 Management of Patients with Advanced Heart Failure in ITU

Management of critically ill HF patients should involve a multidisciplinary team. The intensivists co-ordinate the expertise of different teams to offer maximal benefit for the patient. Basic management starts with appropriate nutrition, mobilisation and physiotherapy. As infection is common in heart failure patients, general antiseptic measures and evidence based antimicrobial treatment is essential. A necessary part of the management is correction of anaemia, electrolyte abnormalities, thyroid and adrenal function, as well as anticoagulation. Psychological and family support is important in patients where life style is likely to be dramatically changed or life expectancy shortened.

Stabilisation of ACHF patients in the ICU provides time to explore treatment options such as heart transplantation and mechanical cardiovascular support, and facilitates decision-making. Cardiac transplantation is an option for a selected subset of patients with ACHF. Common reasons for exclusions are neurological dysfunction, pulmonary hypertension, renal failure, and diabetes with end-organ damage. Some patients with reversible contraindications (e.g. renal dysfunction secondary to HF, pulmonary hypertension associated with high left sided filling pressure) may be rendered transplantable after a period of mechanical circulatory support.

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Simulation in Anaesthesia and Intensive Care

4

Paolo Persona and Carlo Ori

Simulation is a technique to replace or amplify real experiences with guided ones that evoke or replicate substantial aspects of the real world [1]. Another definition of medical simulation said: "a person, device, or set of conditions which attempts to present evaluation problems authentically. The student or trainee is required to respond to the problems as he or she would under natural circumstances. Frequently the trainee receives performance feedback as if he or she were in the real situation" [2]. It can be considered as an attempt to reproduce real or imaginary environments and systems to study the behaviours of the subjects and the consequences of their actions in real time. Despite this definition includes a wide variety of experiential activities, in the medical context the term "simulator" normally refers to a device that presents a simulated patient, or a part of a patient and interacts appropriately with the actions of the participant in the simulation setting.

Development of new technologies, more interest for a different way of teaching, awareness of the importance of continuous medical education moved physicians to consider simulation as a crucial step in the learning process. Anaesthesia seems to be an ideal field where simulation can offer advantages without risks. Till now, students and residents have learned how to intubate, to perform an epidural injection, to resuscitate a patient only 'on the field', including the risk of damages to the patient. Ethic issues, legal quests and the need for more practice to improve surgeons' and anaesthesiologists' skills brought to the development of centres of advanced simulation all around the world, some of these especially dedicated to

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anaesthesiology and critical care. The more we have to improve patient's care, the more simulation centres increase their different and specialistic proposals.

Simulation: WHY?

"Tell me and I forget, teach me and I may remember, involve me and I learn" stated Benjamin Franklin. This is the summary of what is represented in the Learning Pyramid (National Training Laboratories, Bethel, Maine): the retention rates grow from passive teaching methods, like lecture, reading, using of audio-visual support, to the participatory teaching methods like group discussion, practice and the immediate use of the new knowledge. The simulation is located at the basis of the Pyramid and is considered one of the best available way to fix a concept in the learning process.

It is only when something goes wrong that the ability and competence of a physician is bought into question, increasing the culture of blame. The traditional way to teach and learn medicine is still based on junior doctors that have to 'see one and then do one' hoping 'not to harm one' before [3]. New concepts in *medical education* consider more structured and planned curricula and the need to gain and to maintain competence in all aspects of clinical practice. Simulation not only referred to new practitioners. It offers a way to evaluate individual performance, to improve personal skills, and also to test the ability of a team to solve a problem. The concept of Crew resource management was developed by the aviation industry in 1970 and transferred to medicine changed into *Crisis resource management*. It refers to the ability, during an emergency, to translate knowledge of what needs to be done into effective real world activity [4]. It includes also non technical skills as communication, leadership, situational awareness and teamwork. In 1999, the US Institute of Medicine published a report [5] documenting the extent of the problem of human errors in medicine and challenged the existing view that errors resulted from individual recklessness. Instead they suggested it was faulty systems, processes and conditions that led people to make mistakes or fail to prevent them. Protocols, algorithms, but also *educational programmes* resulted to be the new way to face off the problem of human errors. So simulation probably offers an answer to many teaching and training questions about medicine and primarily anaesthesia learning process. Some institutions as US FDA, American College of Surgeons, American College of Surgeons (ACS), American Board of Anaesthesiologists (ABA) have already required a simulation-based training for some of their qualifications [6]. The American College of Chest Physicians (ACCP) published an Evidence-Based Educational Guidelines about simulation as educational tool [7].

The unsolved question is: does simulation training improve operational performance at the bedside and patient outcome? Many studies have demonstrated the effectiveness of simulation in teaching basic medical knowledge [8], procedural skills [9], teamwork features [10], communication methods, at different level of medical instruction, from students to residents. Despite this, some systematic reviews showed that it is not easy to demonstrate if medical simulation as teaching tool really improves outcome of the patients or if educational outcomes influence

the clinical effectiveness of the interventions [11]. A limit is often represented by the assessment tool chosen to measure the result, that in different studies has not be validated [12]. Moreover, the quality of the published articles in this field is generally weak [13] and is hard to obtain data of good quality to fix clear conclusions [14, 15].

The unquestionable benefit of medical simulation is to provide a safe virtual environment where mistakes are permitted and also considered as an opportunity to teach the trainee the implication of his error and to correct and organise his future behaviour [16]. Some errors are inevitable, but living errors in a simulation setting can allow participants to improve their emotional control and to have a better management of the situation if it happens again with live patients [17]. Avoiding 'learning on the job', in simulation settings patients can suffer injuries and even death due to management or practical errors. Participants can discuss their faults in a briefing session and be more prudent to face off the same problem in the real life. The ability to react carefully in an expected situation is one of the most critical factor in creating a positive outcome in medical emergency. Furthermore simulation allows to deal with unusual and complex situations or clinical conditions seldom or never observed in a lifetime. These peculiar features led some authors to define simulation-based medical education as an ethical imperative [18].

Simulation HOW?

The concept that simulator is the basis of a simulation centre is almost dangerous. Simulator is only a tool and, whenever it could be complex and advanced, it needs a team, time, competence and, first of all, a good project. So, once you know what you want to do (curriculum), where you want to do, then buy your simulator.

Educational technologies in medical simulation are divided into three categories: Web-based education, virtual reality and human patient simulation [19]. The Web-based simulation, or e-learning, includes also some experience of simulation of a different way of life. Second Life is a world created on the net where some avatars act as real individuals; it has been used as educational tool in medical field [20], implementing the ability to manage a medical problem in a virtual society.

Virtual reality reproduces a realistic not-real world where is possible to interact with the ambient and subjects mimicking usual and unusual clinical settings. Medical simulation can also be performed in a computer-based way: a simulated scenario is created by a software and the participant tries to solve some quests as in a videogame. It is called microsimulation [21]. The main advantage of this approach to simulation is the possibility to create an unlimited number of scenarios but the participants are often less involved in the action.

The human patient simulation refers to the use of high fidelity simulators that reproduce human patients or part of them. There are a huge amount of simulators in the market that can simulate almost everything. The term 'simulator' generally refers to technology that recreates full environment where to carry out some tasks, but simulation can be performed also using a doll on the floor or a picture of a patient. It depends on the topics that you want to teach. Different simulators were

created and marketed from the first 1960 [22, 23]. The first modern simulator was Resusci-Anne (Laerdal®), a half body of a girl intended for chest compression and ventilation. The last and most advanced one is the Human Patient Simulator (HPS) (METI®), specifically designed for training in anaesthesia, respiratory and critical care. It has the ability to provide continuous gas exchange analysis and haemodynamic monitoring using real physiological clinical monitors. HPS is able to measure the partial pressure of oxygen, carbon dioxide and nitrogen in its lungs, and, based on that, it calculates a real-time blood gas analysis using a mathematical formula. To perform such complex features, it needs a dedicated room with a control deck, a medical gas supplier, a hydro-pneumatic system and a lot of space. HPS can simulate almost every kind of patient because of its ability to set physiological parameters as arterial elastance, baroceptors sensitivity, lungs or chest wall compliance, pulmonary oxygen shunt, volume responsiveness and more over. It can recognise more than 150 different drugs by an identifying bar code and modulate pharmacological effects based on age, weight, physical or haemodynamic conditions. Each parameter can be measured and HPS reacts to physical or mechanical stimuli (photomotor eye reflex) in a physiological way. It can be defibrillated using a real defibrillator machine.

The key word in human patient simulation is 'realism' [24, 25]: the more the participant involves himself in clinical scenario, the more he learns from it. Concerning on this topic, the recreated ambient is also crucial: an operatory room, an emergency department, an intensive care unit must be as realistic as possible, promoting the interaction of trainers with objects.

To perform a simulation project, a simulator is not enough. The main part of the knowledge process during a simulation course is the debriefing session. After the simulated scenario, participants discuss their performance in a plenary session: each clinical choice can be analysed referring on clinical guidelines; mistakes can be underlined and corrected. This step needs a video-recording system and a screen to project the previous recorded performance, according to the latest assumptions about the debriefing session [26]. Trainee can look at his choices and behaviours from a different point of view and can analyse it in a critical way. The combination of brief frontal lessons, micro- and macro-simulations and a debriefing session can probably result in the best way to enhance the strength of a topic during a medical course.

Simulation: WHAT?

Everything can be simulated. Using micro- and macro-simulation, it is possible to create courses about anaesthesia (aortic clamping, anaphylaxis, malignant hyperthermia…), critical care (septic shock, extracorporeal membrane oxygenation management, infections control, …), emergency (basic, advanced and trauma life support, …), communication and more. It is possible to explain the pharmacokinetic and pharmacodynamic proprieties of a drug using microsimulation and to verify its clinical effects in a macro-simulation scenario. The neonatal resuscitation algorithm can be performed in the safest way using neonatal simulator [27]. A rapid access to trachea in a can't ventilate-can't intubate scenario can be obtained

without any risk for the patient. The communication of a tragic event, as a brain-death, can be approached by any medical student facing a simulated crying relative.

Simulation is also a research field where is possible to test new way of teaching [28], new medical devices, behaviours or human beings dealing with stressful or unusual situations. A new device intended for emergency transtracheal ventilation can be tested on a high fidelity human patient simulator measuring continuous blood gas analysis and average tidal volume ventilation [29].

Simulation WHO?

The staff of a simulation centre is the core of the project. In a medical simulation, knowledge, experience and hours of training are needed to get the best performance on stage. Otherwise, the hidden work in the backstage by administrative and audio–video technicians is crucial to manage a simulation medical course. The activity of a simulation centre can be addressed to academic education supplementing frontal lessons with simulated sessions for student or residents; or it can involve physicians and nurses/technicians to improve their knowledge or to refresh some main topics. The ability of tutors to perform as actors, to guide the participant in a foreign ambient, to understand the limits of clinical skill and to discuss the way to overcome these limits, are important feature for the success of a simulation course.

4.1 Fundraising

A simulation project is an expensive project. Money is needed not only to buy a simulator, to build or to arrange the ideal space where to perform the action. They are needed to keep on with the activity considering the staff and the service costs. A good manager must plan a financial project to let a simulation centre to survive. A solution to the problem could be to address a part of the activity to private company: for example, some drugs, medical devices or monitoring systems could be better understood in their application by physicians if explained in a simulated setting. Other solutions could concern European grants for educational or research projects in medical simulation. It's hard to begin, but it is harder to keep it on.

4.2 Simularti

Simularti is the simulation project of Institute of Anaesthesiology and Intensive Care of Padova (Italy). It was born in 2007 and has performed more than 120 medical courses, trained 1,234 physicians on more than 25 topics on anaesthesia and intensive care medicine. Participants came from Veneto region (28.9 %), other Italian regions (52.3 %), and 45 different countries (18.8 %) as China, India, Brasil, Germany, Russia and more over. Furthermore, medical students and

Fig. 4.1 Scenario of the course: coagulation disorders during major surgery

residents of Padova University can change theoric concepts into practical activity, supplementing frontal lessons with simulation scenarios (Fig. 4.1).

The centre is equipped with METI HPS, Laerdal SimMan and SimBaby, different difficult airway training simulators, epidural and spinal trainers, echo-fast simulator and a new transthoracic and transesophageal echocardiac simulator (Heartworks, UK). The last one is a new simulator intended to teach and improve the use of echocardiography by visualisation of ultrasound cardiac image next to a 3D heart model. The difficult in reconstruction 3D cardiac anatomy from 2D slices can be overcome by this simulator [30]. The simulation centre applies a multidisciplinary

approach to the medical simulation, encouraging the collaboration between different specialists as paediatrics, cardiologists, radiologists, pneumologists.

4.3 Conclusion

Simulation technology is a powerful tool for the education of physicians and other healthcare professionals at all levels.

Evidence-based education and training are the new basis of medical educational programs. Simulation will never replace the interactions learned through experience with real patients but it is a powerful and effective educational tool to maximize physician and other health professional training [2]. The cost-effectiveness of a simulation-based medical educational program must be considered in terms of improvement of clinical competence, patient safety and error reduction in the era of limited resources [31].

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Part II
Trauma

Trauma Care Organisation

5

Roderick Mackenzie, Simon Lewis and Basil F. Matta

5.1 Introduction

Trauma is the condition caused by physical injury. Trauma severity ranges from simple self-limiting minor injury to complex, life changing and life threatening major trauma. Severity is most frequently classified using the Injury Severity Score (ISS) with the threshold for 'severe injury' generally accepted as an ISS > 8 and the threshold for 'major trauma' as an ISS > 15. Worldwide, the individual, societal and population consequences of severe injury and major trauma are enormous—to the extent that the World Health Organisation (WHO) consider trauma as a global public health problem [1]. In England, despite a sophisticated and well-developed emergency medical system, organisation of care for more severe injuries has historically been inadequate. As a consequence, the government recently committed to the development of regional systems of care for trauma. In this review, we describe the process for trauma care organisation in the East of England, one of the largest English regions.

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5.2 Drivers for Change

Although the care of major trauma patients in England has been criticised by professional bodies as being disorganised and under-resourced for over 20 years [2–8], the 2007 National Confidential Enquiry is considered as the landmark event in trauma care re-configuration [9]. Entitled 'Trauma: Who cares?', its impact in the UK could be regarded as mirroring that of the 1966 US National Academy of Sciences White Paper entitled 'Accidental disease and disability: the neglected disease of modern society' [10]. The 'Trauma: Who Cares?' report was based on a prospective nation-wide observational study of 795 consecutive patients over a 3 month period with ISS > 15 who survived to reach hospital. It concluded that:

- Almost 60 % of these patients received a standard of care that was considered 'less than good practice'.
- There were deficiencies in the organisation of pre-hospital care, Emergency Department (ED) trauma teams and in-hospital care.
- Incorrect clinical decisions together with a lack of appreciation of the severity and urgency of illness were considered a principle cause of poor quality care. Many of these clinical issues related to both a lack of seniority and a lack of experience of the staff involved.
- Most hospitals managed less than one severely injured patient per week: the average ED with 60,000 new patient attendances a year treats approximately one ISS > 15 patient a week.
- Patients were more likely to receive good care in larger multi-specialty hospitals that were receiving a higher volume of cases.
- There was no method of routinely identifying trauma cases and quantifying the demand for trauma care. Many hospitals did not, for example, submit any data to the UK's national trauma register, the Trauma Audit and Research Network (TARN).

Following the publication of '*Trauma: Who Cares?*', the National Audit Office (NAO), an organisation that scrutinises public spending on behalf of the UK Government, initiated a review of major trauma care [11]. While supporting the findings of '*Trauma: Who Cares?*', the NAO also provided cost data and again challenged the government to introduce urgent change. The NAO estimated health system actual costs of £0.3–£0.4 billion and a further £3.3–£3.7 billion in costs related to lost economic output [11–14]. In contrast, the finance required to optimise existing infrastructure and implement a nation-wide organised system for trauma care similar to those established in many developed countries was considered to be of the order of £70 million [14].

These two national reports also re-stated the evidence from organised systems in other countries that have shown sustained improvements in mortality and morbidity [14–19]. Evidence from reviews of preventable deaths, hospital trauma register studies and population-based studies in these and other developed systems show a consistent 5–15 % reduction in mortality and morbidity [14, 19–24]. What is particularly striking is the evidence that even within well-developed healthcare

systems, authorities who make modest investments in trauma care organisation experience reduced mortality when compared to similarly resourced authorities who do not. Nathens et al. for example [23, 24] used population-based data to examine the effects of organised trauma care in 50 states of the United States and demonstrated an 8 % reduction in overall trauma mortality, including pre-hospital deaths, for those states with organised systems for trauma care compared to those without.

The resurgence of interest in trauma care generated by these reports, together with the resulting professional, political, and public pressure, led the Department of Health in England to commence a process of introducing organised trauma systems. A National Clinical Director was appointed and the National Health Service (NHS) Clinical Advisory Groups (NCAG) were formed [11, 25]. Their recommendations reflected the deficiencies in the current systems and were comprehensive and far reaching (Table 5.1). The regionalization of trauma care was then incorporated into the Operating Framework for the NHS in England: the framework that sets out the business planning arrangements for the NHS and provides the legal and financial framework for service delivery.

5.3 The East of England

The East of England (EoE) has a population of approx. 5.7 million spread across 19,000 sq km (7,335 sq miles) with a tenfold variation in population density and a diverse range of urban, semi-rural, rural and remote settings. The region includes the counties of Bedfordshire, Cambridgeshire, Essex, Hertfordshire, Norfolk and Suffolk and there are wide variations in ethnic diversity, social deprivation and income. Ethnic diversity ranges from highly diverse communities in the cities to much less diverse communities in rural areas. The region also contains some of the most and least deprived 20 % of all areas in England. The emergency medical system is well established with 12 NHS commissioning authorities, 18 major acute hospitals with EDs and a single regional land ambulance service (Fig. 5.1). There are also a large number of voluntary sector and professional organisations with an interest and role in trauma care in the pre-hospital, hospital and community phases of care—including three community funded air ambulance services operating five helicopters. Following the publication of '*Trauma: Who Cares?*', a regional EoE working group was formed to review trauma care and make recommendations for improvement. A baseline survey conducted by the group in 2009 revealed that despite widespread awareness about '*Trauma: Who cares?*', care in the EoE remained poorly co-ordinated, with a lack of clarity around pathways and a paucity of data and understanding regarding patient outcomes. Sixty percent of EoE hospitals still did not, for example, contribute data to the national TARN register and many did not have a Trauma Committee or quality improvement programme in place. The common explanation for this deficit was that major trauma represented less than 0.1 % of total ED activity in each hospital [11, 25]. However, the

Table 5.1 NHS clinical advisory groups (NCAG) recommendations for regional networks for major trauma

Ref	Recommendation
(a) Pre-hospital NCAG	
1	Patients involved in major trauma will be identified accurately and rapidly following their injury. Trauma triage tools should be used to identify such patients
2	A paramedic will be present in the Ambulance Control room 24 h a day
3	Patients with injuries suggestive of major trauma should be taken to the Major Trauma Centre (MTC). Those who are within 45 min travelling time from the centre, should be taken there directly, bypassing other units
4	Some patients will be further than 45 min travel from a MTC; or be trapped; or will have an injury pattern or airway compromise that means that enhanced care needs to be provided [by an Enhanced Care Team or Trauma Unit (TU)] before they can get to the MTC
5	[Physician staffed] Enhanced Care teams will be available 24/7 to provide care to the major trauma patient
6	Patients with major trauma who are taken to a local TU should be transferred to a MTC after initial assessment and optimisation in the Emergency Department (ED)
7	The patient's onward journey and reception should be safe, efficient and planned. All involved in these transfers should work to agreed protocols and be specifically trained and equipped for their task
8	A consultant level doctor with extensive pre-hospital experience of the management of major trauma should be available 24/7 to provide advice on the way to provide the best care for an individual patient
9	Patients who need urgent definitive care at the MTC and those with a serious head injury should be transferred without delay
10	Secondary ED transfer to a MTC should be provided by an appropriately trained team
11	EDs should be pre-alerted of the arrival of patients with major trauma. On arrival at the hospital, a structured handover should be given to the pre-assembled receiving trauma team
12	Regular auditing should be carried out to assess the nature and quality of pre-alert
13	A structured checklist and standardised documentation should be used and included in the patient's clinical record
14	All components of the Trauma Network including pre-hospital services should be mandated to submit data for all Major Trauma patients to a National Trauma Dataset [TARN]

(continued)

Table 5.1 (continued)

Ref	Recommendation
(b) Acute care NCAG	
1	There will be a pre-alert system with effective communication between pre-hospital and in-hospital teams and documented criteria for trauma team activation and patient handover
2	There will be a trained trauma team present 24 h a day for the immediate reception of the patient. The team leader should be a consultant in the MTC and at least ST4 (PGY6) or equivalent competency in the TU. There should be surgical and resuscitative thoracotomy capability within the receiving trauma team
3	There will be 24-hour access to a fully staffed and equipped emergency theatre
4	We recommend for Emergency Radiology facilities:
	(a) CT should be co-located in the emergency department. For patients who are stable, whole-body CT scanning should be provided
	(b) MRI scanning should be available 24 h a day at MTCs
	(c) There should be agreed timelines and competencies for reporting and documentation
	(d) There should be agreed teleradiology facilities between all TUs and the MTC within a network
5	We recommend for Emergency Trauma Surgery:
	(a) This should be performed by a consultant surgeon with appropriate skills and experience
	(b) All surgeons must understand the principles and techniques of damage control surgery
	(c) All patients requiring acute intervention for haemorrhage control must be in a definitive management area (operating room or intervention [radiology] suite) within 60 min of arrival
6	General surgery and orthopaedic surgery senior trainees should be on-site 24 h a day
7	For the acute management of injuries, consultants should be available within 30 min
8	Vascular and cardiothoracic consultants should be available for consultation to the trauma network 24 h a day. A consultant should be available within 30 min at the MTC
9	At MTCs, interventional radiology capability must be available within 60 min 24 h a day. Interventional suites should be ideally co-located with operating rooms and/or resuscitation suites
10	Neurosurgery consultants should be available for consultation to the trauma network 24 h a day. A consultant should be available within 30 min and a senior trainee on-site at the MTC

(continued)

Table 5.1 (continued)

Ref	Recommendation
11	Patients with severe head or spinal injury should be managed in a neurosciences centre, irrespective of the need for surgical intervention. They will be transferred to a specialist spinal centre at the earliest opportunity following full assessment and management as required of co existing injuries
12	Network protocols should assure the safe rapid transfer of patients to specialist care. The ensuring effective referral and transfer is the responsibility of the neurosciences centre. The key point here is to ensure responsibility and ownership, which currently is imprecise leading to inconsistency
13	A consultant should be involved in all decisions to operate for traumatic brain injury. Patients requiring acute neurosurgical intervention should receive this within 4 h of injury and 1 h of arriving in the MTC
14	There will be a network protocol for assessing the whole spine in patients with major trauma. Spinal imaging and assessment should be completed and reviewed by an appropriate consultant within 24 h of admission
15	Appropriate major haemorrhage protocols should be in place across the network and activations regularly audited. In the major trauma centre, a clinical transfusion lead and a transfusion specialist should be available for advice 24 h a day
16	Intensive care units should be on-site and comply with minimum generic standards of the Intensive Care Society and Department of Health
17	[Secondary] transfers should be appropriately staffed and effected in a timely and safe manner
(c) Ongoing care and reconstruction NCAG	
1	Across networks there should be a focus on delivery of patient centred services, which consider all of the health and well-being needs of people who have sustained traumatic injuries
2	The important role of family and friends should be acknowledged and actively supported
3	The ongoing care and reconstruction phase of the trauma patient's pathway should start immediately after any urgent surgery, performed immediately following admission and continue until discharge from the acute setting
4	Coordination of medical, nursing and rehabilitation packages of care is crucial, in both major trauma centres and TUs
	(a) Within TUs, patient care should be overseen by speciality teams with a designated responsible consultant for each patient
	(b) Within major trauma centres, patients' care should be overseen and coordinated by a Trauma Service. The trauma service should include a care and rehabilitation coordinator
5	In the MTC, patients with multiple injuries should be located within dedicated trauma wards

(continued)

Table 5.1 (continued)

Ref	Recommendation
6	In MTCs there should be 24 hour availability of imaging including CT, MRI, ultrasound, interventional radiology and angiography
7	In TUs there should be there should be 24 hour availability of CT scanning facilities
8	Across networks there should be universal access to imaging and Picture Archiving and Communications Systems (PACS). All network organisations should use compatible systems
9	In MTCs, there should be dedicated, separate, fully resourced daytime operating theatres for trauma and reconstructive surgery
10	In MTCs, there should be 24 h care from dedicated intensive care consultants with experience in trauma management and full multidisciplinary support
11	Critical care units should form part of a constituted critical care network and subscribe to a nationally recognised audit process
12	All patients who are admitted to hospital following traumatic injury should be reviewed to establish if they have any rehabilitation needs
13	MTC rehabilitation focused services should be enhanced to ensure delivery of rehabilitation that can meet major trauma patients' complex needs
14	TUs should have the required skills and capacity to ensure they can deliver the rehabilitation required by those patients admitted directly and those who are appropriately repatriated
15	All hospitals taking trauma patients should have a specialist acute pain service
16	Definitive planned surgery for amputations should be performed in consultation with rehabilitation and prosthetic services
17	The prevention of complications arising from spinal instability or neurological compromise must begin immediately and involve all members of the multi-disciplinary team:
	(a) Opinions should be sought from neurology and neuroradiology with a clear definition of areas of clinical responsibility amongst the various neurological specialties
	(b) If there is significant spinal cord injury, early contact should be made with a spinal cord injury centre for advice and to plan strategy
18	A discharge summary describing the patient's injuries, care received and ongoing needs and plans should be provided at the time of discharge or transfer from a MTC or TU. This should include a rehabilitation prescription
19	There should be cross network agreements and adequate resources to ensure that once specialist medical care has been completed, patients can be transferred to the care of a service which is able to meet their ongoing care and rehabilitation needs
20	Any hospital receiving trauma patients should have associated governance structures in place

(continued)

Table 5.1 (continued)

Ref	Recommendation
(d) Rehabilitation NCAG	
1	Rehabilitation should start as soon as is appropriate after admission, typically in the critical care setting, and continue at the intensity required, and for as long as is necessary, to enable patients to achieve their functional potential
2	Patients who have not been admitted to a MTC should not be disadvantaged in accessing the level of rehabilitation they require
3	The delivery of effective rehabilitation following injury should include three key principles: access, coordination and provision and resources
4	All stages of care, including the rehabilitation and transfer aspects of the patient's pathway, should be the responsibility of the network
5	There should be an appointment of a Clinical Lead for Acute Trauma Rehabilitation Services in every MTC
6	There should be adequately skilled and resourced multi-disciplinary rehabilitation teams in all of a network's services
7	There should be rehabilitation and care coordinator posts throughout the network
8	Every patient should receive routine screening of rehabilitation needs
9	A rehabilitation prescription should be provided to all trauma patients with identified needs
10	Trauma patients should receive appropriate levels of care and rehabilitation at all points along their care pathway
11	Many trauma patients are of working age and vocational rehabilitation should, therefore, be a key component of rehabilitation
12	There should be a country-wide review of all services providing rehabilitation to patients who have sustained traumatic injuries
13	A directory of services and resources should be developed relating to rehabilitation and ongoing care to facilitate referral and access to these services
14	Appropriate funding structures should be developed to ensure timely and comprehensive rehabilitation
15	There should be coordinated development of rehabilitation services and long-term support in the community, which can deliver comprehensive and effective rehabilitation to meet the needs of traumatically injured patients, irrespective of their age
16	There should be a review of the applicability of the UK National Dataset for Specialist Rehabilitation Services to all major trauma patients

(continued)

Table 5.1 (continued)

Ref	Recommendation
(e) Network organisation NCAG	
1	The NHS should establish inclusive regional Trauma Systems across England
2	Commissioners should require MTCs and TUs to meet and maintain nationally accepted designation criteria and monitor this compliance
3	Commissioners should ensure that adequately resourced teams to manage the establishment of Trauma Systems are in place via appropriate contracting arrangements
4	The boundaries of Trauma Systems and Networks should be based on the needs of patients, not on NHS structures
5	Networks should take responsibility for the transfer of patients between member units, enforcing appropriate standards at each stage of the patient journey
6	MTCs must be prepared to accept immediate patient transfers without prior warning
7	Network coordinators should be available 24/7 to manage the transfer of patients between providers, as part of the clinical co-ordination function
8	Submission of full, accurate data to TARN should be compulsory for all trauma care providers
9	Each System should implement a Performance Framework to underpin Quality Improvement and to provide assurance to commissioners
10	Trauma Systems should have Quality Improvement programmes operating at all levels
11	Trauma Systems should be actively engaged in injury prevention
12	Trauma Networks should be integrated into Emergency Planning, which should take account of the changes in hospital status caused by regionalisation
13	Injury research should be integrated into the provision of trauma care
14	A National Trauma Board should be established

combination of political, professional and public pressure, combined with the mandate and financial support provided by the NHS Operating Framework ensured that despite these low numbers, there remained a moral, professional and financial imperative to introduce a system of care designed to meet the needs of these patients.

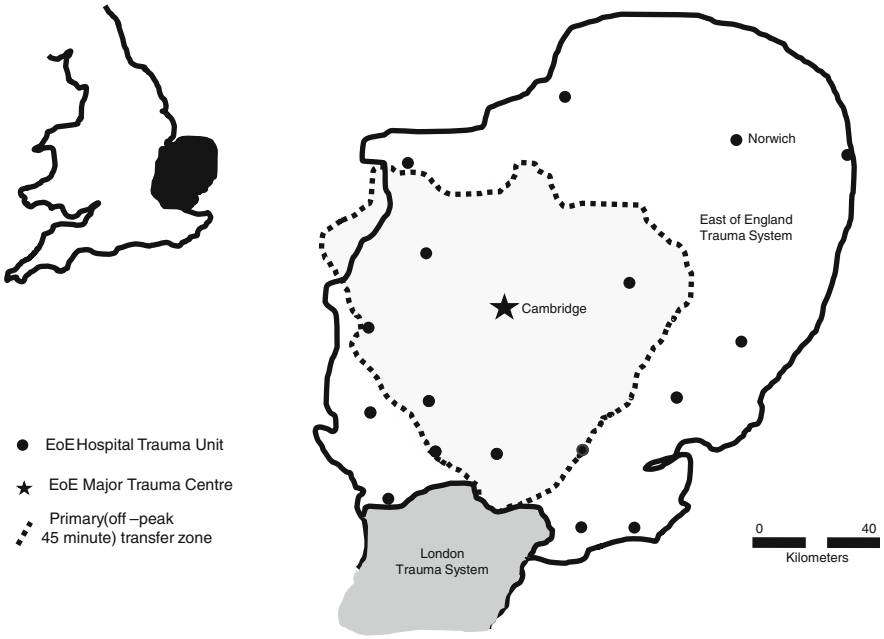

Fig. 5.1 The East of England. The figure shows the location of the acute hospitals (*black circles*) and the major trauma centre (*black star*). Forty five minutes off peak drive time limit on this map (*broken line*) was generated using averaged road segment speeds from ITIS Holdings Cellular based Floating Vehicle Data (CFVD®)

5.4 Developing the Trauma System

A trauma system integrates prevention, pre-hospital care, acute care, reconstruction, rehabilitation and re-ablement in a structured and organised way that optimises resources, care and outcomes. The American College of Surgeons (ACS), The Australasian College of Surgeons and the WHO have all disseminated clear guidance for developing trauma systems [1, 17, 26]. This guidance effectively formed the basis of the NCAG recommendations on regional trauma networks in England (Table 5.1) [25]. In considering the organisation of our system, and the lessons identified, it is useful to use the ACS structure—with the caveat that our trauma system was being developed within an existing established emergency medical system (Table 5.2).

Table 5.2 ACS structure for elements in developing a trauma system [26]

Establish legislative authority
Create an enabling body
Gain stakeholder engagement and support
Quantify the magnitude of the problem
Create a trauma system plan to meet demand
Articulate and agree standards for optimal care
Designate facilities and services
Evaluate the system

5.4.1 Establish Legislative Authority

In any healthcare system design or re-design, there is a need to establish the appropriate level of legislative authority with regard to resource distribution, reimbursement, performance criteria and governance arrangements. The NHS is funded from national taxation and is accountable to the UK Government Department of Health. There is legislation in place related to the responsibilities of the Department and the functions of each element of the NHS, including Ambulance Services and Acute Hospitals as well as healthcare commissioning bodies. Once the Department of Health conceded that organised trauma systems were required and included this in the NHS Operating Framework, the regional needs assessment, planning and commissioning process could commence with legitimate authority. We were fortunate to be in a position to exploit this national focus on trauma care but it is important to consider the extensive historical evidence and the professional and public lobbying that resulted in '*Trauma: Who Cares?*' being added to the National Confidential Enquiry portfolio and drawn to the attention of the National Audit Office. Without these catalysts, particularly in a publicly funded healthcare system in a challenging financial climate, it would not have been possible to proceed. We would encourage those without trauma systems to continue to collect and disseminate evidence and lobby their relevant political and professional groups such that trauma care remains high on the political agenda.

5.4.2 Create an Enabling Body

The ACS recommend the establishment of a strong advisory body composed of health care, medical and public representatives with the credibility, legitimacy and authority to operate the system, develop and enforce standards, designate facilities and ensure the provision of appropriate services. At an early stage, we were able to support the development of a regional integrated trauma system project board which included wide representation from healthcare commissioners as well as provider organisations. In addition, individuals whose expertise, ideas and

behaviours characterised them as opinion leaders were invited to join the board. The terms of reference and membership of the project board were made widely available. To ensure that all aspects of trauma care would be addressed, from pre-hospital through to rehabilitation, the membership of the board was also divided into five work groups that mirrored the five NCAGs (Table 5.1). This structure and membership provided reassurance that hospitals, services and communities that might be affected by trauma system organisation would be properly represented. Commissioning funds were used to support the board and provide the core staffing for a Trauma Network Office (TNO); comprising a Network Director, a regional Clinical Director for acute care, a regional Clinical Director for rehabilitation, a Network Manager and the necessary administrative support staff. The creation of this new administrative entity was challenged but defended on the basis that trauma system design and implementation on such a scale needed adequate resources. In addition, there were many commissioner and provider relationships to be managed across the existing system and there was a need for a focal point for effective information and communication exchange. The TNO, as the enabling body, has been critical to the success of our system design and implementation.

5.4.3 Gain Stakeholder Engagement and Support

It is essential that there is community-wide engagement in trauma system development, particularly if it may be perceived that either resources will be redistributed or that patients and families will have to travel longer distances. In addition to the NHS healthcare organisations in the region, there are 58 national government (parliamentary) constituencies and 11 major local government authorities with statutory health overview and scrutiny responsibilities. The TNO developed a consultation and communication strategy that engaged public, political, professional and patient groups throughout the region and with neighbouring regions. The strategy included information and education, public surveys, a 'Surviving Major Trauma' branded information campaign (through a variety of media), dedicated stakeholder events and a website. The neighbouring London trauma system had already started to develop and we were also able to benefit from the communications and public engagement strategy already implemented there [27]. Key to success was that communications were underpinned by a clearly articulated case for change that could be disseminated by a number of public and professional champions. From the outset, it was also important to emphasise that, based on EoE geography and the evidence available from previous service re-configurations (such as Cancer, Percutaneous Coronary Intervention and Stroke services), the aim was to create a system designed to care for all injured patients and involve all services and facilities. Assurances were provided that there would not be whole scale re-distribution of resources or displacement of patients and that the trauma care organisation would exploit existing regional strengths, be sustainable over time and result in improved outcomes.

5.4.4 Quantify the Magnitude of the Problem

As with any other disease process, the planning of prevention and treatment strategies requires a good understanding of the magnitude of the problem and the causes, distribution and determinants of disease in the population. Injury epidemiology has, however, been a relatively neglected field in the UK and there remains a paucity of meaningful population-based data to guide local service re-configuration—compounded by a range of legal, regulatory and ethical barriers to effective data sharing [28]. Available estimates of the incidence of major trauma ranged from 7.3 to 33 per 100,000 population depending on the definitions used [6, 9, 11, 29–32]. The uncertainty surrounding the true incidence was reflected in guidance published by the Intercollegiate Group on Trauma Standards [32]. While acknowledging that "The exact numbers of major trauma patients in England are unknown due to lack of robust population-based data collection," the group recommended planning for 27–33 ISS > 15 survivors to hospital per 1,00,000 population per year. For the EoE, this would equal an upper range of 1,881 ISS > 15 patients a year [32].

We were fortunate that we were able to access a local sub-regional population-based injury research register (the Cambridgeshire Trauma Audit and Research Project—CTARP) and compare these published estimates with historical hospital-based activity data submitted to TARN by our institution and other parts of the UK [33]. CTARP data was derived from the local population with 100 % case ascertainment and appeared to more closely reflect our experience. The CTARP rate was based on actual cases, rather than estimates, over a 5-year period (2000–2004). In contrast, TARN estimates were projected cases based on averaged 2003–2007 core hospital returns (only four of which were EoE hospitals). In the context of planning services, these differences are not mere semantics: CTARP estimated that there would be 12.1 cases per 1,00,000 population or 692 ISS > 15 survivors to hospital in a year, whereas TARN estimated that there would be 15.4 cases per 1,00,000 population or 880 patients in a year [33].

Using the CTARP data, we were able to determine a directly age-standardised rate (using the European Standard Population) for the range of fatal and serious injury for all ages as 55 per 1,00,000 residents (95 % CI 52.6–57.4). This rate reflects the overall burden of trauma on the entire emergency medical system. This overall rate masks the complexity of the distribution of disease on different components of the system. The hospitals, for example, are not required to respond to the 500 or so pre-hospital deaths but the ambulance service clearly is Fig. 5.2 shows the distribution of age-standardised rates of different severity of injury across the whole population. It can be seen that in terms of planning for true major trauma, our estimated rate of survivors to hospital with an ISS > 15 was approximately 650–750 patients. Based on the evidence in the literature, these are the patients who are most likely to benefit from trauma care organisation and treatment in a specialist multi-disciplinary hospital or major trauma centre (MTC). Quantifying the magnitude of the problem allowed us to explore the gap between

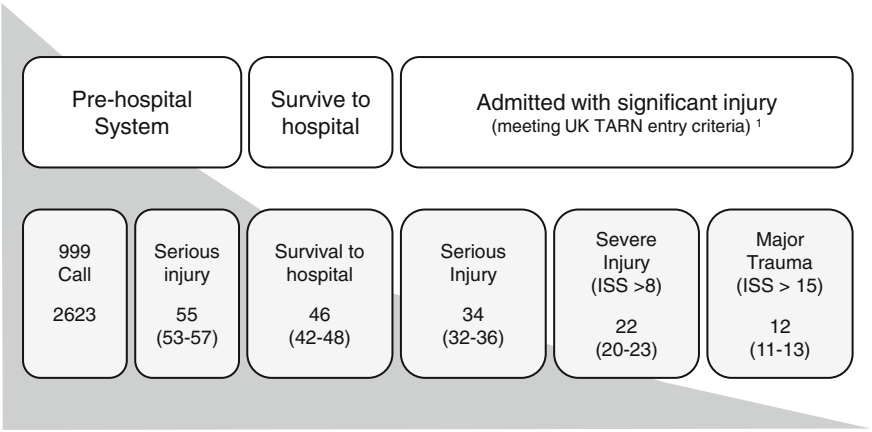

Fig. 5.2 Overall burden of disease (Count of patients, 95 % CI). See www.tarn.ac.uk for details of TARN entry criteria. Rates are directly age-standardised rates per 100,000 resident population with 95 % confidence interval. 999(111) Ambulance calls based on estimate from NHS Ambulance Service related to call burden for trauma related medical priority dispatch codes (150,000/year)

available resources and the anticipated needs for different models of trauma system and consider how to ensure that these ISS > 15 patients accessed appropriate care.

5.4.5 Create a Trauma System Plan

The fundamental premise underpinning a trauma system is that all patients with major trauma should be managed in a specialist hospital with access to the full range of specialist services and a significant case load. The optimum case load for a hospital to develop and maintain optimal skills is thought to be of the order of 400–600 cases a year [34]. The implication is that there is only sufficient case volume to justify one major trauma centre in the EoE. This is particularly the case when net outward movement of patients at the periphery of the region into neighbouring trauma systems (and MTCs) is taken into account—approximately 20 % of cases from the more heavily populated areas close to London. Within the EoE, there was also only one existing multi-disciplinary specialist hospital (Cambridge University Hospitals—CUH) which could fulfill the role. CUH was already a regional centre for neurosurgery, some elements of specialist surgery (e.g. hepatobiliary) and paediatric intensive care. Had we not taken local epidemiology into account, we might have planned for additional MTC capacity.

NCAG agreed by consensus that a journey time of up to 45 min from scene of injury to ED would reflect an acceptable balance between risk and benefit for major trauma patients (Table 5.1). Figure 5.1 illustrates the 45 min drive time threshold (utilizing real time data) from CUH. Approximately, 1.35 million people

live within 45 min of CUH. If all patients who are considered to be potential major trauma patients are taken directly to CUH from within that area, then the primary (from scene) major trauma activity estimates for CUH can be estimated (Table 5.3). The population of 4.35 million who are outside the 45 min drive time now present a challenge. Although patients could potentially be conveyed from these areas to the MTC within a 45 min journey by helicopter, the community-funded helicopter services in the EoE do not operate in poor weather or the hours of darkness and do not form the core emergency ambulance service. It was therefore necessary to design a system that would allow patients who lived beyond 45 min journey time to be taken primarily to the nearest ED when helicopter services were not available and then, as necessary, transferred secondarily to the MTC at CUH. These considerations led to the adoption of the inclusive trauma system model.

There are two broad conceptual models for trauma system design. These 'inclusive' or 'exclusive' models differ, in the simplest terms, with respect to the extent to which all components of the emergency medical system (and wider health care system) are involved and engaged. In 'exclusive' systems, the focus is predominantly on the resources of the MTCs. The underpinning philosophy is that all patients with suspected major trauma within the area covered by the MTC will be primarily transferred there from the scene, bypassing all other facilities. Exclusive systems save lives and are ideally suited for urban areas or where helicopter resources can be guaranteed. In contrast, an 'inclusive' system is better suited to more dispersed populations and geography where primary transfer to the MTC is not necessarily a safe or publicly acceptable option. In well-developed inclusive trauma systems, all acute hospitals participate and arrangements are put

Table 5.3 East of England major trauma activity estimates (annual count of patients with 95 % confidence interval)

Area	Pre-hospital system		Hospital system	Admitted with significant injury (meeting TARN entry criteria)		
	999 (111) calls	Serious injury	Survival to hospital	Serious injury (TARN criteria)	Severe injury ISS > 8	Major trauma ISS > 15
Residents less than 45 min drive time from EoE MTC (pop 1,365,700)	3592	751 (724–778)	628 (574–655)	464 (437–492)	300 (273–314)	164 (150–178)
Residents more than 45 min drive time from EoE MTC (pop 4,351,700)	114145	2393 (2306–2480)	2002 (1828–2089)	1480 (1393–1567)	957 (870–1001)	522 (479–566)

Note that 20–25 % of patients who are more than 45 min from the EoE MTC are within 45 min of a London Trauma System MTC

in place to support and monitor the range of facilities at each hospital and the bypass and secondary transfer arrangements that underpin the system. A well-designed inclusive system, which takes a population rather than an institutional perspective, also saves lives [35]. There are, however, some implications for system design with inclusive systems—including the need to co-ordinate patient movements across the network, provide outreach education, medical support and retrieval and manage a wider range of organisations and professionals.

We utilised data on times of presentation and patterns of injury from CTARP and TARN to develop a better understanding of the trauma epidemiology in the EoE. This knowledge, combined with a 45 min time/distance-based threshold for the likely primary (from scene) and secondary (from hospital) transfer activity allowed us to model patient flows and appreciate the associated resource implications. We were then able to outline the basic components of the trauma system: a TNO, a single regional ambulance service supported by three air ambulance services, a single regional MTC and a managed clinical network of acute hospitals with 24 h EDs which would be designated as Trauma Units (TUs) and supported by MTC co-ordination, outreach and transfer services.

Having described these basic system components, we then modelled the impact of varying the thresholds for primary/secondary transfer triage decision making. This led to a detailed review of field triage tools used by pre-hospital personnel to identify potential major trauma patients. NCAG had recommended the adoption of a UK modified version of the ACS Guidelines for Field Triage [25, 36]. This system has four elements: physiological derangement, anatomical injury, mechanism of injury and special circumstances. However, early experience of the use of this tool in the London trauma system had led to significant over-triage rates. Although full data was not available, only 317 (29 %) of 1,088 patents who triggered the tool were found to have an ISS > 15 in that system [37]. This is consistent with the original ACS under and over-triage rates (of 5–10 and 30–50 %, respectively) and is considered acceptable in an urban environment with short travel times. We were concerned the effects of introducing this tool in the EoE on ambulance and patient disposition, journey lengths and capacity at the MTC. A review of the literature and the London experience identified that the physiologic parameters in the tool gave the most accurate triage followed by the anatomic parameters. Mechanism, co-morbidities and the judgement of field personnel performed least well. We, therefore, developed a triage decision support tool with the TNO and Ambulance Service that focused solely on physiological and anatomical parameters. The key aspects of this new triage tool were:

(a) The Glasgow Coma Scale (GCS) score criteria were simplified to the motor component only and the threshold increased. In terms of predicting important clinical outcomes (such as emergency intubation, clinically significant traumatic brain injury, need for neurosurgical intervention, and mortality), the GCS motor score alone has demonstrated a similar test performance when compared with the total GCS score. Furthermore, a simplified motor score which collapses the 6-point motor component of the GCS to a 3-point Simplified Motor Score (Table 5.4) has been shown to perform equally well [38–40].

Table 5.4 Simplified GCS motor score

Patient response to stimulus	Glasgow coma scale (GCS) motor score	Simplified motor score
6	Obeys commands	Obeys commands
5	Localises painful stimuli	Localises pain
4	Flexion/Withdrawal to painful stimuli	Withdrawal to pain (or less)
3	Abnormal flexion to painful stimuli (decorticate response)	–
2	Extension to painful stimuli (decerebrate response)	–
1	Makes no movements	–

(b) The anatomical parameters were made explicit. In particular, those related to suspected pelvic and skull fractures (Table 5.5).
(c) Penetrating trauma and burns were removed with pre-hospital personnel advised that these should be managed initially by local EDs.
(d) Mechanism and Special considerations criteria were removed.

On completion of this triage tool review and agreement on the criteria (Table 5.5), we were then able to articulate the concept of operations in more detail (Table 5.6) and further refine the system components (Table 5.7).

5.4.6 Articulate and Agree Standards for Optimal Care

Once the system design and concept of operations were determined, detailed specifications for organisations and clinical services could be further developed. NCAG articulated a range of standards based on WHO and ACS guidance together with experience gained in UK systems (Table 5.1). These standards were reviewed in detail by the project board and discussed widely amongst stakeholders. Whilst many reflected evidence-based practice and common sense, many also represented a change in clinical or operational practice which would require both a culture and a resource change. The most striking examples related to the seniority of decision makers and the tempo of decision making—both factors which were clearly identified by '*Trauma: Who Cares?*' Despite the challenges, gap analyses based on activity modelling and the criteria in the performance framework were submitted by each provider and service specifications were then incorporated into the NHS contracts for each service (all hospitals and the ambulance service). This contractual framework provided the basis for performance management of each component of the system—something that had not previously been possible in the context of trauma care.

Table 5.5 Pre-hospital identification of major trauma—East of England field triage decision tool

Step 1: Measure vital signs and level of consciousness
If a patient is involved in serious injury event and/or with suspected major trauma triggers any single criteria, pre-hospital personnel must notify control of 'major trauma patient' and, if within a 45 min drive time for a MTC and ABC's are manageable, transport directly to MTC. Otherwise the patient should be taken to the nearest ED (TU)
• Sustained respiratory rate below 10 bpm or above 29 bpm (use age specific values for children)
• Sustained systolic blood pressure below 90 mmHg or absent radial pulses (use age specific values for children)
• GCS (Motor) Score of 4 or less (i.e. withdrawal to pain or less)
Proceed to step 2 if physiology normal. Irrespective of whether physiological parameters triggered, notify control if patient trapped or enhanced scene care likely to be required (e.g. for analgesia, sedation, clinical care)
Step 2: Assess anatomical injury (only if physiology normal)
Look for clinical signs in the list below. If any are present, then pre-hospital personnel must notify control of 'major trauma patient' and, if within a 45 min drive time for a MTC and ABC's are manageable, transport directly to MTC. Otherwise the patient should be taken to the nearest ED (TU)
(a) Flail chest or open chest wound
(b) Suspected major pelvic fracture
i. Pain in the pelvic area, including the lower back, groin and hips. in the alert, cooperative patient
ii. Pelvic deformity
iii. Bruising or swelling over the bony prominences, pubis, perineum or scrotum
iv. Leg-length discrepancy or rotational deformity of a lower limb (without fracture in that extremity)
v. Wounds over the pelvis or bleeding from the patient's rectum, vagina or urethra
(c) Suspected open or depressed skull fracture
i. Severe pain associated with scalp injury and local haematoma in the alert, cooperative patient
ii. Depressed or deformed area of skull
iii. Open scalp wound with visible bone fragments
iv. Signs of a basal skull fracture (peri-orbital bruising, mastoid bruising, bleeding from nose and/or ears, sub-conjunctival haemorrhages)
v. Head injury with focal neurological deficit
(d) Crushed, degloved, mangled or amputated limb
(e) More than one fractured proximal long bone
(g) Neck or back injury with paralysis
Note that patients with penetrating injuries and patients with burns who do not trigger the triage tool should be taken to the nearest ED

Table 5.6 The concept of operations for the EoE trauma system

1.	All major trauma patients should be managed in a MTC
2.	All persons involved in serious injury events and attended by the Ambulance Service should have the EoE field major trauma decision tool (field triage tool) applied by the first attending Ambulance personnel
3.	Ambulance Control should be informed of all patients who trigger the field triage tool and who are therefore candidate major trauma patients. Ambulance Control should then immediately notify the Network Co-ordination Service, who will co-ordinate receiving hospitals and, where necessary, an outreach retrieval and transfer service
4.	All patients who trigger the decision tool within a 45 min journey time from the EoE MTC should be transferred directly to the EoE MTC unless they are considered to be closer to an alternative MTC. The Network Co-ordination Service will be able to provide advice and will ensure that the appropriate MTC has capacity and is pre-alerted
5.	All patients who trigger the decision tool but who are more than 45 min from a MTC should be discussed with the duty Consultant at the Network Co-ordination Service. The expectation is that they will be transferred to the nearest TU but it may be appropriate to undertake an extended primary transfer
6.	All patients who are first assessed in a TU will undergo rapid initial assessment by a senior doctor according to agreed regional trauma system policies and procedures. Damage control resuscitation will be initiated and Computed Tomography (CT) will, wherever possible, be carried out and reported within 30 min of arrival. Consultation with the MTC, including image transfer, will take place regarding optimisation of clinical care and transfer decisions within 60 min
7.	Patients who are considered suitable for management in the TU will remain there. Patients with complex injury which doesn't require transfer to the MTC but which exceeds the capabilities of the TU will be transferred to the appropriate specialist hospital in the region. The Network Co-ordination Service will facilitate both the consultation and the transfer
8.	If emergent patient transfer is indicated, either to the MTC or to another specialist service, the Network Co-ordination Service will facilitate referral, mobilise an outreach retrieval and transfer service and co-ordinate transfer
9.	The Network Co-ordination Service will ensure that rehabilitation services and processes have been activated for all major trauma patients and pass details of the clinical case to the Trauma Network Office
10.	The Trauma Network Office will, through pre-agreed region wide information sharing and clinical governance arrangements, collate data related to major trauma care, interpret national TARN data, facilitate regional education and outreach training, manage the services provided by the Network Co-ordination and MTC outreach retrieval and transfer services and provide activity and performance reports to commissioners

5.4.7 Designate Facilities and Services

The ACS has significantly advanced the care of the injured in North America by creating and promulgating the Advanced Trauma Life Support course, publishing Resources for Optimal Care of the Injured Patient [26] and defining a process for system verification and hospital designation. The process undertaken by the TNO—stakeholder engagement, activity modelling, gap analyses and negotiation

Table 5.7 East of England trauma system components

1. A region wide hospital trauma network encompassing a single MTC and the seventeen acute hospitals in the region with type 1 (major) emergency departments who have been designated as Trauma Units
2. Clearly defined processes for:
(a) Rapid identification of potential major trauma patients by Ambulance Service personnel (using a field triage tool and policy)
(b) Rapid access to specialist on-scene and in-transit medical support to the Ambulance Service (using outreach retrieval and transfer services)
(c) Supporting primary transfer of potential major trauma patients from the scene to a MTC if within 45 min travelling time, bypassing Trauma Units if safe to do so
(d) Immediate consultant clinical decision support and advice by telephone for Ambulance Service, Outreach Service and TU staff for patients who are unstable or trapped or more than 45 min travelling time from a MTC
(e) Supporting primary transfer from the scene to a TU for unstable patients and those who are more than 45 min travelling time from a MTC
(f) Immediate senior clinical assessment, rapid CT scanning and early consultation with the MTC for potential major trauma patients who are primarily taken to TUs
(g) Supporting early secondary transfer of major trauma patients from TUs to the MTC
(h) Ensuring early identification of rehabilitation needs and initiation of rehabilitation
(f) Co-ordination of all trauma system activity via a network co-ordination service
3. A regional Major Trauma Outreach Service capable of primary and secondary retrieval by land or air and staffed by specialist paramedics, nurses and physicians
4. A regional Network Co-ordination Service which co-ordinates patient journeys and access to services from the point of injury to rehabilitation
5. A regional Trauma Network Office which provides the network management and governance functions, interprets regional TARN Data and manages the education and outreach elements of the system

of a financial and performance framework effectively constituted an initial hospital designation process. For many hospitals in the EoE, there was not the option of choosing not to be designated given their geographical distribution (relative isolation) and existing responsibilities and workload. The TNO nonetheless initiated a programme of peer review/verification and only formally designated hospitals as TUs on demonstration of achievement (or ability to achieve) the NCAG recommendations. This process of peer review/verification relates to a review of individual facilities regarding their provision of key elements of trauma care, including human resources (e.g., availability of appropriately qualified and/or senior personnel), physical resources (equipment and space) and administrative and governance functions, such as Trauma Committees and quality assurance functions. We found that this whole process also established the authority of the TNO as the entity with an overarching responsibility across all hospitals in the system.

5.4.8 Evaluate the System

The EoE Trauma Network became fully operational in August 2012 and the performance and quality framework is now being applied. We hope to soon be in a position to review the performance of the system and start to understand the impact on care. In order to achieve this, we have ensured that all hospitals now submit data to the national trauma register (TARN) and have created a new, more process focused, regional trauma patient management system to both support case management and capture data on injuries, interventions and outcomes. Once the system is more mature, and our co-ordination, outreach and transfer services are fully established, we intend to also seek external peer review and accreditation.

5.5 Summary

The clinical vision for the EoE was to develop an integrated and inclusive range of trauma care provision. After 3 years of planning and negotiation, the EoE Trauma Network went live in August 2012. We have been fortunate to be in a position to learn from the experience and efforts of other systems at a time when political and professional aspirations were aligned. Although the anticipated benefits of the system are unlikely to be fully realised for 5–10 years, we have already seen a marked change in the seniority and tempo of decision making, particularly with respect to secondary inter-hospital transfers. There are of course many threats to the system at this early stage. These include threats to system finance and political and professional support as well as pressures caused by a changing demographic and further re-configurations of the NHS. We are confident, however, that we have created a resilient system which can achieve the trauma system benefits shown in established international systems, save many lives, reduce disability and improve overall health outcomes.

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Part III
Cardiovascular System

Cardiovascular Risk in Non-cardiac Surgery

6

Luca Ferdinando Lorini and Lorenzo Filippo Mantovani

6.1 Introduction

The past three decades have seen an increasing demand for surgery procedures (both elective and emergencies) in an elderly population. Moreover the huge advances in cardiac therapeutic treatments (coronary percutaneous revascularization, the advent of electrophysiology procedures for the treatment of arrhythmias, and new drugs for cardiac diseases) led to an increase in the cardiac disease population: nowadays, the challenge for the anesthesiologist is to cope with a population more aged and affected by cardiac disease. It is estimated that in the EU perioperative life threatening cardiac complication related to non-cardiac surgical procedure on heart disease patients could reach an average of 200,000 cases every year [1].

Three main factors play a critical role in the decision-making process to evaluate the heart disease patient scheduled for a non-cardiac surgery procedure:
(1) Type and extent of cardiac disease
(2) Type of scheduled surgery
(3) Co-existing disease.

Type and extent of cardiac disease: Type of cardiac disease can greatly influence the outcome of patients undergoing surgical procedure; between the many aspect of cardiology implication of the patients we can identify three major

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types of affections: ischemic cardiac disease, valvular disease, chronic heart failure disease.

Ischemic cardiac disease: This group of patients is divided in two further subgroups: stable ischemic disease and unstable ischemic disease patients. Only two large trials [2] explored the outcome for patients scheduled for non-cardiac surgery with stable conditions (CARP and DECREASE-V). A prophylactic strategy of preventive myocardial revascularization is not mandatory unless for specific cases undergoing high-risk surgery (i.e., aortic and major vascular surgery and peripheral vascular surgery). Those cases should be discussed on a multidisciplinary basis prior surgery. Emergency surgery comes first anyway. All the other kind of surgery of lower risk should be not postponed to revascularization. Obviously a subsequent revascularization strategy will follow surgery according to existing guidelines when needed.

In case of unstable cardiac ischemic disease, especially in acute coronary syndromes, surgery should be postponed when possible, in the unlikely case of concomitant emergency surgery and acute coronary syndrome, surgery comes first anyway. In this case strategy of revascularization should be the percutaneous one according preference to PCI alone or bare metal stents placement and subsequent surgery as soon as possible (usually 3 months or earlier if necessary). A pharmacologic strategy should be associated too (anti-platelets drug, β blockers, and when necessary anticoagulant therapy).

Valvular disease: Among the valvular affections the most dangerous one is aortic stenosis, unfortunately, this kind of disease is the commonest one in current surgery population. In case of severe aortic stenosis (valvular area <1 cm or 0.6 cm^2/m^2 BSA) clinical condition of patient should be evaluated: symptomatic patients undergoing elective surgery should be offered chance of prophylactic aortic valve replacement prior to non-cardiac surgery. Patients who refuse or are not eligible should be considered for a percutaneous valve implantation or at least balloon aortic valvuloplasty. This strategy should be considered even in case of asymptomatic patients scheduled for high-risk surgery. Asymptomatic patients scheduled for intermediate or low-risk surgery can be treated in a conservative manner. High-risk surgery can be performed only in patients not eligible for aortic replacement only if really needed and under strict hemodynamic monitoring.

Mitral stenosis: This kind of disease does not preclude surgery especially low and intermediate risk ones. Symptomatic patients with significant mitral stenosis (area <1.5 cm^2) associated with pulmonary hypertension (i.e., PAP $>$ 50 mm Hg) should be considered for preventive percutaneous mitral commissurotomy or open surgical valve repair especially if scheduled for high-risk surgical procedures.

Aortic and mitral regurgitation: This kind of affection usually does not affect perioperative course unless there is concomitant presence of poor left ventricular function (i.e., EF $<$ 30 %) those patients should be strictly hemodynamically monitored and pharmacological therapy should be optimized carefully before surgical procedure. High-risk surgery procedures should be considered only if necessary.

Chronic heart failure: Since long time, presence of chronic heart failure disease has been associated with increased adverse perioperative outcome. An old study showed a significant relationship between low EF (<35 %) and postoperative adverse cardiac events [3]. Left ventricular function seems not to be prognostic to define perioperative risk but more accurate could be the actual NYHA class of patient. This kind of patients remains at high risk of perioperative complications. Accurate perioperative hemodynamic monitoring and optimization of preoperative cardiologic therapies seems to be the optimal choice to reduce risk of adverse events in this subgroup population.

Type of scheduled surgery: Although patient-specific clinical state is a major factor in the evaluation of perioperative risk, type of scheduled surgery has historically been recognized as a very important factor too in predicting the prognosis for non-cardiac surgery procedures on cardiac patient. According to type of surgery, procedures are divided in three branches [4]:

(1) Low-risk procedures
(2) Intermediate risk procedures
(3) High-risk procedures.

Risk has been determinate as probability of acute myocardial infarction and cardiac death within 30 days of surgery. The only surgical high-risk procedures (>5 % of probability of event) are vascular ones (major surgery on aorta and vascular peripheral procedures) all other kind of surgery could be considered as intermediate or low-risk procedures (ranging from less than 1 to 5 % risk ratio). Moreover extensive studies demonstrate that not only vascular surgical procedures are most likely to have perioperative cardiac adverse events but this population is best suited to ameliorate by good anesthetic management. Specialist cardiac evaluation before urgent surgical procedures (i.e., abdominal aortic rupture) do not obviously improve outcome, and could only dangerously delay timing of surgery, but a good pre-operative patient evaluation is mandatory before elective surgery.

Classical studies led to identification of clinical perioperative risk factors (Lee index and Erasmus model) [5]. The most recent investigation led to evidence that five independent risk factors can strongly affect perioperative outcome: pre-existing ischemic heart disease (angina, previous MI), chronic heart failure, history of stroke or transient ischemic attack, chronic renal failure on dialysis or acute renal failure. Those factors associated with type of surgery should led to a more accurate preoperative assessment of scheduled patients. A simple and well-recognized method for first line evaluation of patient is determination of his metabolic (METs) capacity. Clumsily evaluation of inability to climb two flights of stairs is considered below the four METs capacity and is strongly associated with high cardiac risk. We should recognize that this tool is a poor one; we can only say that a good METs capacity (6–10) is associated with very low risk but under the five METs threshold we have to evaluate strictly the associated risk factors and type of surgery. In conclusion: evaluating the patient by means of type of surgery, preoperative risk factors, and clinical evaluation (METs) is a simple and very fast method to obtain an initial good stratification, but there is a warning to carefully investigate those patients falling under the five threshold.

Co existing diseases: Four co-existing diseases are independent risk factors for adverse perioperative outcome. They are: renal disease (functional), cerebrovascular disease, pulmonary disease (especially COPD and pulmonary hypertension), and diabetes mellitus.

Renal disease: A low renal function is a strong factor for perioperative risk of adverse cardiovascular event. It is included in most of preoperative risk scores. Two features seems to be important in evaluating those kind of patients. Preoperative values of creatinine clearance and worsening of the renal function after the surgical procedure. It seems a value of creatinine clearance lower than 64 ml/min or a serum creatinine more than 2 mg/dl should be associated with a worst outcome [6]. In the presence of previous kidney dysfunction, seven independent preoperative factors have been identified: liver disease, emergency procedure, high BMI, advanced age, arterial peripheral disease, and COPD under pharmacological treatment with bronchodilators. In the preoperative setting, there is strong evidence of the negative influence of contrast-induced nephropathy due to preoperative radiological examinations (very frequently executed in cardiac patients), this kind of disease benefits of a preoperative treatment with isotonic sodium chloride is associated with or not with oral N-acetyl cysteine.

Cerebrovascular disease: There is a strong incidence of this kind of pathology in the aging population, typical features of the disease are previous history of Stroke or TIA. Postoperatively appearance of stroke or TIA is strongly associated with adverse outcome but even more subtle events like delirium, anxiety, or depression are often expression of CNS lesion. The major mechanism of CNS damage seems to be more an embolic event than ischemia due to hypoperfusion per se and discontinuation of anti-platelet or anticoagulant therapies is to be undesirable if possible, those agents should not be discontinued as far as possible even during intraoperative period. The most risky situation is a recent event of cerebrovascular stroke or TIA and further investigation should be pursued in this situation.

Pulmonary disease: Even if the presence of a pulmonary disease enhances the risk of generic perioperative complication, only two specific entities are associated with an increased risk of cardiac adverse event during surgery: those are COPD and pulmonary hypertension. COPD is loosely associated with a generic increase of perioperative cardiac event and is seldom included in the key factors of preoperative risk, even the definition of COPD seems to change from study to study, the main feature associated with the increased risk should be the FEV1 reduction and it seems there is a linear association with cardiovascular risk. Pulmonary hypertension is a rare acquired or idiopathic condition, it is an incurable disease and it is associated with increase rate of adverse cardiac event in the perioperative period, especially in terms of heart failure and ischemic complications. In both cases the first line treatment should be aimed to optimize pharmacological treatments prior to surgery and to maintain perioperative measures like inodilatative support.

Diabetes mellitus: Diabetes and mere extensively altered glucose control are a common finding in cardiac patients undergoing surgery. Not only diabetes promotes atherosclerosis and cardiovascular disease in the chronic setting but it can destabilize and accelerate pre-existing stable coronary disease, since 2001 there has been an increasing interest in perioperative strategies aimed to control or at least to smooth hyperglycaemia [7], despite promising initial results some considerations are to take in account. First a strict perioperative and more over intraoperative control of values of glycemia often request a continuous infusion of insulin, this kind of treatment could be harmful, especially during general anesthesia and need careful monitoring of level of blood glucose to avoid dangerous hypoglycemia. Nowadays, we accept that correct strategy should aim to control acute changes in levels of blood glucose more than avoid hyperglycemia. It seems that desirable levels of glucose should be around or lower than 200–180 mg/dl, this target is more easily to obtain during the perioperative period taking account of stress-induced hyperglycemia, furthermore it seems reasonable to apply this kind of control by means of insulin infusion only in protected environment (ICU).

Anesthesia issues: The intraoperative workload of anesthesiologist should be eminently committed to a careful monitoring of real cardiac function and to prevention of acute worsening of hemodynamic; this is often obtained by means of maintenance of patient's homeostasis. Contrary to common belief, at the present, there is no evidence about a real superiority of a single anesthesia technique in this field. Neither regarding inhalation versus intravenous general anesthesia nor general versus loco-regional or combined techniques, nevertheless there is a certain agreement to grant a preference to combined or loco-regional anesthesia whenever possible due to its intrinsic better control of perioperative pain and ability to lower sympathetic stimulation. This factor seems to be important in decreasing neuro-humoral adverse activity, a factor that could elicit adverse cardiac event due to increase stress. On the other side, loco-regional anesthesia has an intrinsic and unavoidable risk when performed under anticoagulation and or disaggregating therapies.

Anticoagulation and anti-platelet drugs have seen a widespread use in the last decade; this is due to the explosion of intracoronary stents utilization and endovascular procedures. This kind of drugs is going to be of great influence on choice of anesthetic techniques and decision-making strategies in the perioperative period.

Greatly affected by this therapies is the field of loco-regional anesthesia, especially the neuraxial techniques, this is due to the increased risk of catastrophic neurological events in presence of abnormal bleeding status. According to literature, anticoagulant therapy with dicumarols can be safely replaced with low weight molecular heparin (LWMH) shortly before surgical procedures making loco-regional techniques safe, unless particularly clinical situation, this change of therapy is well tolerated and scarcely associated with severe thrombotic events. In specific cases, a continuous infusion of intravenous heparin can be discontinued shortly before surgery allowing any kind of anesthesia (loco-regional or general). Great attention is due to timing of removal of epidural catheters, usually allowing a

free time from anticoagulation of 12–24 h and laboratory tests monitoring according to literature.

More challenging is the anti-aggregating scenario. The "stent invasion" is creating an increasing number of patients under single or even double anti-aggregating therapy, we know well that even a brief suspension of this kind of therapies can lead to dramatic adverse cardiovascular events. We now know that a safe neuraxial technique can be safely performed in patients under ASA alone according to recent literature, unfortunately there are not extensive studies about postoperative bleeding in patients under double anti-aggregating therapies or on therapies with the newest agents. Furthermore an increasing number of anti-platelet drugs, with different mechanism of action, are coming in the next future, thanks to increased research in this field under the pressure of cardiovascular new techniques. In this scenario, the latest studies confirm it is very dangerous to stop anti-platelet therapy so we suggest performing a general anesthesia technique. In some elective highly selected patients at high risk of stent thrombosis and/or perioperative bleeding use of preoperative intravenous short half life GPIIb/IIIa receptor inhibitors as a "bridge" has been proposed [8].

Anyway, surgical intraoperative bleeding under anti-platelet drugs have been overrated in the past. A reasonable approach to this problem could be, beyond an accurate surgical hemostasis, the utilization of internal clinical protocols based on "point of care" technologies aiming to evaluate the coagulation pathway (TEG®, ROTEM®), and\or the platelets activity (Multiplate®, Verify now®, TEG PTI®, PFA 100®).

The event of persistent postoperative bleeding in patients with intracoronary stents and under double anti-platelet therapy or new anti-platelet agent is still poorly evaluated in recent literature. Anyway administration of platelets seem to be not contraindicated in such case and seem to be a reasonable approach to the problem, even in this situation, possibility of access to platelet function laboratory test can help the clinician to monitor the real platelet function status of the patient and better aim his therapeutic strategies.

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Part IV
Kidney

Continuous Renal Replacement Therapy: Challenges and Evidences

7

Giorgio Berlot and Antoinette Agbedjro

7.1 Introduction

The aetiology of the Acute Kidney Injury (AKI) in critically ill patients admitted to the Intensive Care Unit (ICU), and especially in those with sepsis and sepsis-related Multiple Organ Dysfunction Syndrome (MODS), is multifactorial, being variably associated with hypovolemia, the use of nephrotoxic substances including some classes of antibiotics and radiologic contrast media and the production and release of a number of mediators occurring during the host-infecting agent interaction [1–3]. According to the balance between pro- and anti-inflammatory mediators, the final effect can range from a relatively localized process (i.e. pneumonia) to a devastating systemic process [4, 5], related to the individual genetic predisposition [5]. The final clinical scenario includes the exhaustion of all reactive capabilities ultimately leading to immunoparalysis and death [2]. The kidney is commonly involved in sepsis, as its function can be compromised either directly by the very same mediators acting in other organs and indirectly due to their systemic hemodynamic effect [6].

Independently from the cause(s), the occurrence of AKI is associated with a worse prognosis as compared to AKI-free patients [1]. In the early 1980s the Renal Replacement Treatments (RRT) of critically ill patients with AKI was revolutionised by the introduction of techniques based on the convective transport of water and solutes, as opposed to the diffusive process which is suited for intermittent haemodialysis (IHD) [7]. The fluid removed by convection (a) is qualitatively iso-osmotic with the blood and contains equal amount of electrolytes; and

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(b) is quantitatively replaced by water and solutes deriving from the extracellular space thus reducing, albeit not eliminating at all, the cardiovascular disturbances associated with IHD. As the former treatments are supposed to run on a 24-h basis they are collectively known as Continuous Renal Replacement Therapy (CRRT) to differentiate from Intermittent Renal Treatments (IRT), which include the IHD and the Slow Low Efficiency Dialysis (SLED) and whose durations are much shorter. Since then, a number of modifications to the initial technique, which was based on the patient's own arterial pressure, have been developed, including the interposition of a roller pump and a negative pressure in the extracorporeal circuit, making thus the procedure independent from the patient's hemodynamic conditions (Continuous Veno-Venous Hemofiltration-CVVH) [8]. Further developments included mainly (a) the exchange of elevated volumes of fluids (High Volume Continuous Veno-Venous Hemofiltration-CHVVVH); and (b) the association of diffusion to the convection, leading to the Continuous Veno-Venous Hemodiafiltration (CVVHD) (Table 7.1) [8]. The large popularity of these techniques is mainly due to the relatively good hemodynamic tolerance in critically ill patients, which has been ascribed to the diffusive transport. In the same period, as it became clear that the molecular weight (MW) of the sepsis mediators was compatible with their passage through the membrane used in CRRT, indeed, several investigators hypothesized that these techniques could treat at the same time the cause and the effects of the sepsis-associated AKI by removing these substances and by eliminating the uremic toxins [9, 10]. Since then on, the CRRT has been used either with renal as well as non-renal indications, being these latter addressed more at the removal of septic mediators than to the treatment of AKI-associated derangements. However, in most studies published on its use in critically ill patients, it is difficult to separate one effect from the other.

7.2 Experimental Evidence

As far as the non-renal indications are concerned, the CRRT could be valuable in the neutralization of sepsis mediators provided that:

(a) Their MW lies within the cut-off value of the membrane used, thus causing their removal through the filter down in the collecting bag where they can be measured in the ultrafiltrate (UF), whose production for unit of time (Qf) becomes the key factor [8, 9];
(b) as an alternative, the mediators can be removed from the blood circulating inside the chosen CRRT by their adsorption on the surface of the filter [11]; of course, this process is time-limited and ceases once the sticking capabilities of the membrane are saturated;
(c) the filtered molecule(s) must constitute the active form of a given mediator: as an example, although the MW of monomeric TNF is 17,000 kD, the biologically active form is trimeric, thus exceeding the cut-off of most of the commercially available filters used in CRRT [12];

Table 7.1 Principal variants of RRTs. Legend: Qb: blood flow, Qf: ultrafiltrate flow

Denomination	Abbreviation	Class	Principle of functioning	Driving forces		Replacement fluid[a]
				Qb	Qf	
Continuous arterio-venous hemofiltration	CAVH	CRRT	Convection	Patients's own arterial pressure	Patients's own arterial pressure	Yes
Slow continuous ultrafiltration	SCUF	CRRT	Convection[a]	Patients's own arterial pressure/roller pump	Patients's own arterial pressure/aspiration	No
Continuous veno-venous hemofiltration	CVVH	CRRT	Convection	Roller pump	Aspiration	Yes
Continuous veno-venous hemodiafiltration	CVVHD	CRRT	Convection + diffusion	Roller pump	Aspiration	Yes
Continuous high-volume venovenous hemofiltration	CHVVVH	CRRT	Convection	Roller pump	Aspiration	Yes
Intemittent hemodyalisis	IHD	IRT	Diffusion	Roller pump	Aspiration	Yes
Sustained low efficiency dialysis	SLED	IRT	Diffusion	Roller pump	Aspiration	Yes

[a] The amount and composition of the replacement fluids vary according to the clinical conditions

(d) they are present in the bloodstream in relevant concentrations when the procedure is running, since both too early or too late treatments can be ineffective: in the former case because the burst of the mediators could not have occurred (yet), whereas in the second because an irreversible end-organ damage could have already occurred [11, 13, 14], making any treatment futile.

Since the reduction in the blood concentration of sepsis mediators represents the ultimate goal of non-renal indications of CRRT, their measurement before and after the initiation of the treatment became the issue addressed by many studies. Indeed, several investigations, aimed to demonstrate an effect of CRRT techniques on the blood values of different inflammatory and counter inflammatory mediators have been carried out, but the overall results were not uniform. The reduction of the blood concentration of septic mediators by means of the techniques commonly used in CRRT has been demonstrated by several investigators, who were also able to demonstrate that healthy animals and/or isolated tissues challenged with the fluid removed from septic organisms undergo similar cardiac, respiratory and metabolic derangements [15–17]. Moreover, it appears that both Qf and time of initiation play a major role, as either the decrease in mediators or the peripheral effect are more marked with higher volumes of UF and when the treatments started in the early phase of sepsis [18–21]. However, other studies failed to confirm these results, as mediators remained stable or even increased [10, 22] during the treatment. To add to the confusion, a substantial hemodynamic improvement was observed in the absence of any change in the blood concentration of the measured mediators [23].

Different factors can account for these somewhat puzzling results. First, inflammatory mediators can be produced during the process itself, due to the interaction between the blood and the membrane [22]; as a matter of fact, this phenomenon accounts for most of the physiologic derangements commonly observed during IHD using less recent membranes [24]. The same consideration applies to the production of inflammatory mediators observed during cardiopulmonary bypass, which, by the way, can be efficiently removed by means of CRRT [25]. Second, the mechanisms responsible for this reduction can differ according to the membrane used: as a consequence, one cannot expect a marked or prolonged decrease in circulating mediators once the adsorptive capabilities of the membrane have been exhausted [10]; the latter being a time-dependent process, it is likely the concentration of septic mediators will show a bimodal course, with an initial decay followed by a subsequent increase [13]. Third, although a substantial reduction in the circulating levels of several mediators, including the Platelet Activating Factor, (PAF), the Tumour Necrosis Factor-α (TNF-α) and various Interleukins, has been demonstrated [15] in different models of sepsis, the impact on the natural history of sepsis may be hard to evaluate since the blood concentrations of septic mediators (a) can fluctuate during the septic challenge (as well as during the clinical course); (b) as stated by Cavaillon [14], their blood values can be considered the tip of an iceberg, poorly reflecting what is going on at the tissue level; and, finally, (c) the biologically active forms of some mediators can be different from that assayed in the UF [12]. Finally, different membranes can exert

different results in terms of neutralization of sepsis mediators: as an example, Rogiers et al. demonstrated that TNF was more efficiently removed by polyacrilonytrile (PAN)-made membrane as compared with polysulphone [26].

7.3 Clinical Evidence

When looking at clinical investigations using CRRT in the treatment of critically ill patients with AKI, some relevant issues arise including:

(a) Is the CRRT superior to IRT in terms of outcome improvement?
(b) Should this be the case, its effect can be entirely ascribed to the removal of mediators or other factors, including a better hemodynamic tolerance compared with IRT, play a role?
(c) Does a dose–response effect exist? and, finally,
(d) Does the timing of initiation of treatment influence the outcome?

As far as the first question is concerned the results of clinical studies carried conflicting results, with older investigations favouring CRRT over IHD, whereas more recent meta-analyses failed to demonstrate any advantage. In a non-recent review Kellum et al. [27] reviewed 13 studies involving 1,400 patients and did not find any significant difference in the overall mortality between CRRT and IRT-treated patients. However, when the six studies in which only patients with comparable severity of illness at time of initiation of the treatment were considered, the outcome was significantly better in those treated with CRRT. Different factors likely accounted for these results, including the heterogeneity of patients included, the causes of AKI, the amount of volume exchanged, the membrane used, the timing of the procedures and the underlying conditions. The author concluded that there is no sufficient evidence to demonstrate definitely a superiority of CRTT over IHD and advocated a large, controlled randomized trial (RCT) encompassing the rules of the Evidence Based Medicine (EBM). In a meta-analysis contemporaneous to the Kellum's one, also Tonelli et al. [28] were unable to demonstrate any superiority of CRRT over IHD in terms of both survival and recovery of renal function in critically ill patients. Other more recent studies that have been completed after the publication of these meta-analyses failed to demonstrate any superiority of CRRT over IRT [29–31]. Yet it should be remarked that some factors other than CRRT could have influenced the results and thus a definitive evaluation on their real efficacy is probably still premature. This issue has been recently discussed by Bagshaw et al. [32] in a meta-analysis which failed to find any superiority of CRTT over IRT. The authors enlighten several factors able to impede to draw definite conclusions. First, the poor quality of many studies, which prompt the authors to evaluate only 9 RCTs out of the 1,550 investigations initially screened. Second, it is likely that more unstable patients could have been treated by means of CRRT which offers clear advantages in terms of cardiovascular stability, thus causing a selection bias [33]. Third, even if an improvement in survival is obvious of exceeding importance when studying a novel approach for sepsis, still it

could be a too hard endpoint if one considers the extreme heterogeneity of sepsis population, whose prognosis can be influenced not only by the acute organ dysfunction(s) but also, if not predominantly, by the underlying conditions, the age, genetic factors predisposing to sepsis and AKI [34, 35] and by therapeutic options other than the type of renal replacement treatment used [36]. Third, the impact of AKI on the outcome is different according to its time of occurrence, being worse when it appears in an advanced stage of a critical condition [37], and in the advanced phases of MODS any kind of treatment unlikely influences the outcome.

The possible effects of the removal of septic mediators are the subject of intense debate. As stated above, most, if not all, the mediators implicated in the septic process can be eliminated through the filter via the convective transport or can be absorbed on the membrane, even if the efficacy of this latter process is subjected to decay. Unfortunately, sepsis appears to be a dynamic process, during which mediators with different properties are produced at the same time. This polymorphism is likely responsible for the repeated negative results of clinical trials aimed to study the effect of the neutralization of a determined mediator [2]. In different time frames, one class of substances can prevail on the other, leading to a systemic inflammatory response syndrome (SIRS), associated or not with an infection, or, conversely, to a status characterized by the progressive blunting, till the exhaustion of this response [2–5, 38]. Although oversimplified, this is a reasonable model to understand the bizarre clinical course of many septic patients, in whom an anergic status often follows, and sometimes concludes, a critical illness initiated with a typical inflammatory process (e.g. pneumonia or peritonitis). Several investigations were addressed to assess the efficacy of CRRT in terms of mediators' removal. Not differently from what has been already described for the outcome, results have been not unequivocal [9, 15]. Again, it should be recalled that, the mediators being involved are subjected to ample individual and time-related variations, the difference observed in many studies could be ascribed to different time frames of initiation of the CRRT itself. In other words, it is unlikely that elevated amounts of TNF, which is a powerful pro-inflammatory cytokine, could be extracted during the advanced phase, in which anti-inflammatory mediators predominate.

The intensity of treatment represents another hot point. Actually, the dose of RRT represents the most important determinant for the control of uraemia in patients with chronic renal failure. Some authors demonstrated that also in sepsis-associated AKI the intensity of the treatment influences the outcome independently of the technique used. In a group of critically ill patients with AKI of different origins Ronco et al. [39] used CRRT performed with different amounts of volume exchanged (20, 35 and 45 ml/kg/h, respectively) and demonstrated a significant reduction in mortality in the group of septic patients more aggressively treated. A dose-dependent improvement of survival has been demonstrated also in another study using high-volume hemofiltration [40]. Almost at the same time, Schiffl et al. [41] demonstrated that daily IHD as compared with IHD performed on an alternate day basis was associated with an improved outcome in a group of critically ill patients with AKI.

Then, from these studies it appears that the outcome is influenced more by the intensity of the treatment than by the treatment in and by itself. Other investigators [42] demonstrated that in critically ill patients with multifactorial AKI receiving CVVH with different Qf (1.0 vs. 1.5 l/h) the more aggressive regimen was associated with a better control of uraemia even if the outcome was not different in the two groups; however, it is clear that in both groups the Qf was much lower than in Ronco's study. More recently, a large observational study involving 553 patients with AKI treated either with CRRT or IHD at different intensities failed to demonstrate any beneficial effects on the outcome by higher dose RRT, although there was a reduction in ICU stay and duration of mechanical ventilation in the more intensely treated patients [43]. In a recent meta analysis, Pannu et al. [44] who scrutinized 38 out of 173 published studies comparing the effect either of the type of treatment and its intensity, concluded that CRTT and IHD are equally effective in the treatment of AKI, but should be a CRTT used, a dose of at least 35 ml/kg/h should be provided.

Also, the issue of the timing of initiation is somehow controversial Similar to other therapeutic approaches recommended in sepsis, including the administration of antibiotics and the achievement of determined hemodynamic goals [45], the timing of initiation of CRRT appears to be a key factor in influencing the outcome of patients with sepsis-associated AKI. Actually, the term "timing" can be misleading, as, according to the study considered, it applies either at a time interval from the diagnosis and to the severity of organ dysfunction at or before the start of CRRT. Piccinni et al. [46] used the Risk Injury Failure Loss and End-stage kidney disease (RIFLE) criteria [47] to subdivide patients with septic shock treated with CVVH and demonstrated a significantly better survival in those treated on the "Acute Renal Injury" phase as compared with those in the "Acute Renal Failure" phase. Similar results have been demonstrated also by other investigators who used pulsed, short-term (4 h) high volume (35 l) hemofiltration followed by CVVH at a standard intensity; responders (patients whose cardiovascular and acid base status improved during the 4 h period) were treated earlier than non-responders and the survival rate was significantly higher in the former (9/11) than in the latter group (0/9) [48]. However, these findings have not been confirmed in another study [49] addressed to elucidate the role of early high volume CVVH compared with early-low volume CVVH and late-low volume CVVH in which the authors failed to demonstrate any difference in "hard" endpoints including 28-days survival and recovery of the renal function. Despite these controversial results, a recent meta-analysis demonstrated that an earlier initiation of RTT could exert a positive effect on the outcome [50]; however, as stated by the authors, once again this conclusion is based on studies of variable quality enrolling patients with AKI from heterogeneous causes.

7.4 Final Considerations

On the basis of the available results, some conclusions can be reached on the role of CRRT techniques for the treatment of sepsis-associated AKI. First, despite roughly 20 % of patients treated with CRRT experiencing arterial hypotension during the procedure [51], yet the principle of functioning confers an advantage in terms of hemodynamic stability, making them suitable also in severely compromised subjects, making CRRT the preferred renal treatment in critically ill patients with AKI [52]. Second, although the results are not uniform, there are suggestions indicating that either an early start of treatment, possibly associated with elevated volumes of exchange can be associated with a better outcome (or of a surrogate of outcome, such as the decreased need for catecholamines to support the hemodynamic functions). This can be summarized and transferred into the clinical practice with "the sooner and the more, the better" concept. Finally, it should be recalled that all meta-analyses take into consideration only a small fraction of the published studies, thus weakening the related conclusions.

7.5 Conclusions

Despite extended experimental and clinical investigations, the role of CRRT in the treatment of sepsis is still under scrutiny. As far as AKI is concerned, despite a better hemodynamic tolerance associated with the convective removal of fluid and solutes, mortality remains high in the treated patients, and the place occupied by IHD is going to be re-evaluated. The feasibility of removal of sepsis mediators is based on sound experimental bases, yet there is no evidence that this feature exerts any major effect on the outcome. It is likely that a more in-depth knowledge of the chemico-physical characteristics of the membranes could be valuable in enhancing the elimination of these substances via their removal with the ultrafiltrate or their absorption on the filter surface by implementing the Qb or the Qf, respectively.

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Part V
Lung

Postoperative Respiratory Complications

8

Maria Vargas, Yuda Sutherasan and Paolo Pelosi

8.1 Introduction

Postoperative Respiratory/Pulmonary Complications are as common as cardiovascular events, occurring in 2.5 % up to 5 % [1]. The incidence of postoperative pulmonary complications (PPCs) varies according to their definition [2]. Respiratory failure from pulmonary or cardiac origin, pneumonia, respiratory infection, pleural effusion, atelectasis, pneumothorax, bronchospasm, need of non-invasive respiratory support or re-intubation have been differently classified as postoperative pulmonary or respiratory complications [3, 4]. The occurrences of PPCs lead to an increase in morbidity, mortality and length of hospital stay. The purpose of this chapter is:

(1) To describe the mechanisms of PPCs
(2) To analyse recent clinical study on this topic
(3) To identify the methods for prevention of PPCs

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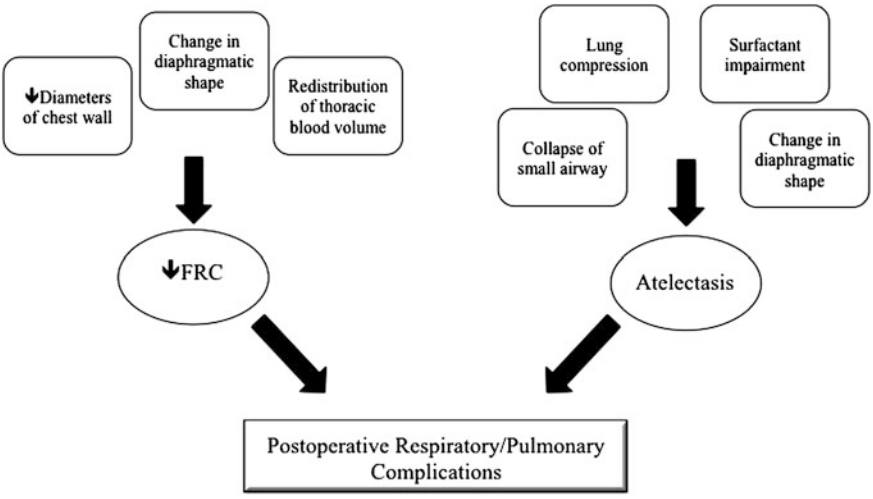

Fig. 8.1 Shows the mechanisms of reduction in residual functional capacity and atelectasis as main responsible of postoperative respiratory/pulmonary complications

8.2 Mechanism of Postoperative Pulmonary/Respiratory Complication

General anaesthesia may affect the respiratory system in different ways resulting in alteration of breathing control, respiratory muscle activity, residual functional capacity, atelectasis and distribution of alveolar ventilation and perfusion [5]. Furthermore, also anaesthetic drugs may affect different areas of nervous system responsible of breathing patterns and respiratory muscle activity [6, 7].

Reduction of functional residual capacity (FRC) during surgery has also been reported in absence of pulmonary comorbidities, such deterioration occurs at the induction of anaesthesia and remains stable during the surgical period [8]. Different mechanisms can explain the reduction of FRC during anaesthesia as reduced diameters of chest wall, change in diaphragmatic shape and position and redistribution of thoracic blood volume. The reduction of thoracic diameters is associated to the reduction of inspiratory muscular tone responsible of an altered recoil mechanism of chest wall. In this condition the internal diameters of ribcage have been reduced with lowering effect on lung volume [9]. Loss of muscle tone and increasing intraabdominal pressure (IAP) may favour a cephalic shift of diaphragm that contributes to a further reduction of FRC. Furthermore, also the controversial effect of the redistribution of thoracic blood volume from the peripheral vessels seems to have a role in the reduction of FRC [10] (Fig. 8.1).

Atelectasis occurs in 90 % of patients underwent general anaesthesia; it is predominantly located in dependent lung zones [11]. Different mechanisms may be responsible for the occurrence of atelectasis during anaesthesia as collapse of small

airway, lung compression, surfactant impairment and redistribution of alveolar gas. The collapse of small airway during general anaesthesia is due to the reduction of closing capacity [12]. Supine position during surgery promotes atelectasis because of the presence of a gradient in transpulmonary pressure associated to the increase of IAP. The alteration of pulmonary and abdominal pressure results in lung compression and collapse [13]. The impairment of lung surfactant causing atelectasis is still controversial. The presence of volatile anaesthetic agents and high inspiratory oxygen fraction may alter the permeability of alveolar barrier and inactivated lung surfactant [14]. The redistribution of intra-alveolar gases in presence of high inspiratory oxygen concentration and of an increase in ventilation/perfusion ratio have been associated to absorption atelectasis that is more markedly with the occurrence of small airway closure [15].

8.3 Clinical Study on Protective Mechanical Ventilation Preventing Postoperative Pulmonary Complication and Outcome

PPCs have been matter of different clinical studies during the last 10 years. Several factors have been hypothesised to play a role in the occurrence of PPCs after surgery as mechanical ventilation.

Although the effect of long-term mechanical ventilation in critically ill patients with acute respiratory distress syndrome (ARDS) has been well established; the effect of short-term mechanical ventilation on lung parenchyma is not clear enough [16].

Furthermore, protective lung ventilation was also associated to a better outcome in patients who do not have ARDS [17].

Although protective mechanical ventilation for patients with ARDS is strongly recommended by international guidelines [18], its application in operation room is still debated.

Wrigge et al. investigated the effect of mechanical ventilation with low (6 ml/kg) and high (12 ml/kg) tidal volume on lung and systemic inflammation during major thoracic and abdominal surgery. As results, the concentrations of pulmonary and systemic mediators of inflammation did not differ between the two groups [19]. The same results were obtained by these authors also in cardiac surgery [20]. In the same years Perez et al. found an increased risk of postoperative respiratory failure in patients undergoing pneumonectomy and ventilated with large tidal volume [21]. Wolthuis et al. investigated the effect of short-term mechanical ventilation with low tidal volume (6 ml/kg) and high positive end-expiratory pressure (PEEP) (10 cm H_2O) in a randomised clinical trial (RCT) [22]. The author concluded that the use of lower tidal volume and high PEEP may limit pulmonary inflammation in patients without pre-existing acute lung injury undergoing elective surgical procedure [22]. The role of PEEP in mechanical ventilation has been evaluated in a non-conclusive Cochrane review [23].

This review, included eight randomised clinical study, showed no difference in mortality and postoperative pulmonary complication in patients ventilated with PEEP in operation room [23]. Severgnini et al. evaluated the impact of protective intraoperative ventilation during open abdominal surgery on a modified Clinical Pulmonary Infection Score (CPIS) and postoperative pulmonary function [24].

As a result, this author found that protective ventilation strategy, although improved the respiratory function and decreased the CPIS, did not affect the length of hospital stay.

According to this promises, the European Society of Anesthesiology proposed some studies evaluating different aspects of perioperative care [25]. The first concluded study is EUSOS (European Surgical Outcomes Study) published in the lancet [26]. EUSOS results showed 4 % mortality after surgery, with the majority of patients dying outside intensive care unit [26]. PERISCOPE (Prospective Evaluation of a Risk Score for Postoperative Pulmonary Complications in Europe) is an on-going study focusing on preoperative pulmonary risk factors to stratify the perioperative management of these patients [27].

PROVHILO (The Protective Ventilation using High versus Low positive end-expiratory pressure), a concluded randomised clinical study with the manuscript under preparation, aimed to investigate the effect of the open lung strategy with high PEEP and recruitment manoeuvres in short-term mechanical ventilation against postoperative pulmonary complications[28]. Finally, LAS VEGAS (Local Assessment of Ventilatory Management during General Anaesthesia for Surgery and its Effects on Postoperative Pulmonary Complications) is an on-going prospective clinical study to assess the current practice of mechanical ventilation during general anaesthesia and its impact on postoperative pulmonary complications [16]. Simultaneously with ESA researches, the University Hospital of Clermont-Ferrand has developed a study, named Intraoperative protective ventilation in abdominal surgery (IMPROVE Study), to compare the effect of lung protective ventilation with conventional ventilation on PPCs. According to this study, protective ventilation was performed with 6–8 ml/kg tidal volume, 6–8 cm H_2O PEEP and recruitment manoeuvres; while conventional ventilation was set with 10–12 ml/kg tidal volume without PEEP. This study has been completed with the enrolment of 400 patients [29]. The IMPROVE study, as randomised clinical evaluation, may clarify the role of protective ventilation on PPCs. Furthermore we think that, PROVHILO may explain the role of high and low PEEP during anaesthesia and LAS VEGAS may define the impact of current practice of mechanical ventilation about the occurrence of PPCs according to their large and planned sample size.

8.4 Methods for Prevention of Postoperative Pulmonary Complications

8.4.1 Identification of At-risk Patients (Possible Role of Different Scores) and WHO/NEJM Checklist

The risk factors associated with PPCs depend on basic underlying status, method of anaesthesia, smoking status, type of surgery and postoperative anaesthetic drugs. Recent large prospective cohort study in Europe has shown an unexpectedly high mortality after major surgery, and high incidence of PPCs has also been demonstrated [26].

Haynes et al. have reported the result of prospective multicentre study after implementation WHO surgical checklist in 3,733 patients undergoing non-cardiac surgery. The authors have demonstrated significant decrease of mortality from 1.5 to 0.8 % and decrease of inpatient postoperative complications from 11 to 7 %. However, this study has not shown the difference of PPCs such as pneumonia [30].

The 2,006 clinical guideline of American college of physician classifies patients' related risk factors namely advanced age, ASA classification of two, chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). About procedure, evidence good support the high risk associated are aortic, thoracic and abdominal surgery [3, 4].

Several investigators realised that the overall risk of PPCs can be predicted and have been developed the different following excellent scores. The difference of various scores consists of simplified factors and also objective factors that can be assessed at bedside.

Role of recently predictive score

Postoperative respiratory failure risk index and pneumonia risk index

Last decades, the investigators from the veterans' affair combined several factors to develop predictive model, already validated, for postoperative respiratory failure in major non-cardiac surgery based on National Surgical Quality Improvement Program (NSQIP) data. Besides the type of surgery, age, functional status and COPD, they added laboratory data including, albumin level less than 30 g/L, and blood urea nitrogen level more than 30 mg/dL in the model. Furthermore, the same investigators constructed the postoperative pneumonia risk index by data from 1,60,805 patients. This index was added the data of impaired sensorium, cerebral vascular accident, transfusion, long-term steroid use, smoking and alcohol use to recent index. However, this index has some limitations in terms of generalizability due to the major part of populations are male veterans and including numerous risk factors in the index thus it is difficult to use in real life clinical practice [31, 32]. These indices were included in meta-analysis and the 2,006 American college of physician guideline.

Postoperative pulmonary complications risk score (ARISCAT group)

A large prospective cohort in 2,464 patients undergoing surgical procedures has demonstrated 5 % of PPCs incidence. The authors have recently identified variables namely preoperative arterial desaturation, preoperative haemoglobin concentration <10 g/dL, recent respiratory infection in the last month that were not included in ACP guideline as a strong predictors. Additionally, the study confirmed that surgical type and duration of procedure are associated with PPCs. The AUCs under ROC curve are 90 and 80 % for the development of PPCs predictive index and the validation of this index, respectively. The promising advantage of this score is based on a simplified assessment and objective variables [2]. Further large European PERISCOPE (Prospective Evaluation of a Risk Score for Postoperative Pulmonary Complications in Europe) study is undergoing and will act as external validation of this score.

The surgical lung injury predictor score (The SLIP score)

Of 4,366 patients, Kor et al. develop the new score for distinguishing patients underwent high risk surgery and need mechanical ventilation during general anaesthesia longer than 3 h who occurred postoperative ARDS from patients who did not. Risk factors in this score consist of high risk cardiac, vascular or thoracic surgery, DM (Diabetes mellitus), COPD, GERD (Gastroesophageal reflux disease) and alcohol abuse. This score can discriminate patients and develop early postoperative ALI from those who did not with AUC of 0.82 (95 % CI 0.78–0.86). However, this study is conducted as a retrospective design that confounds internal bias, single centre and heterogeneity of population [33, 34].

Postoperative respiratory failure (PRF) risk calculator

Regarding the large retrospective NSQIP data set, Gupta et al. have developed the postoperative respiratory failure risk calculator based on logistic regression model. The defined variables consist of surgical procedure, emergency surgery, ASA classification, functional status and sepsis. PRF risk calculator is available online and on mobile application that yields more benefit for physicians [35]. Identifying at-risk patients is a useful tool for optimising proper intervention especially in high risk patients to avoid unnecessary loss of resources and expenditure. The discrepancies among several studies are reasoned by the difference of outcome, risk factor definition and population.

Newly defined risk factors including obstructive sleep apnoea and pulmonary hypertension, not included in previous mentioned indices, affect the postoperative morbidities, thus we may require further study to improve the predictive score performance [3].

8.4.2 Perioperative Respiratory Monitoring

Regarding the advance technology, we have various respiratory monitoring tools in either ICU or operating theatre. Nowadays, physicians have the trend to use less invasive tool.

Basically, anaesthesiologists still widely use pulse oximetry for monitoring hypoxemic events during perioperative period. A large prospective cohort of 2,464 patients undergoing surgical procedures showed that 28.6 % of patients with arterial oxygen saturation ≤90 % (SpO_2) had at least one in-hospital PPCs, therefore preoperative SpO_2 has been included in the ARISCAT score as independent predictor of PPCs [2]. In perioperative care, the pulse oximetry plays a role in detection of hypoxemia and related events, however, these findings have not affected mortality in large trials [36].

The standard method for direct measurement of CO_2 is ABG samplings. The non-invasive measurement such as end tidal CO_2 monitoring can detect circuit leak, circuit disconnection and CO_2 retention during anaesthesia, however, it is limited to use only in mechanical ventilated patients. Recent study investigated the role of continuous non-invasive transcutaneous PCO_2 monitoring ($tcPCO_2$) for analgesic-induced respiratory depression in the intraoperative and postoperative period in patients for whom invasive $PaCO_2$ monitoring would have been indicated. The authors demonstrated significantly higher $tcPCO_2$ in patients receiving intravenous opioid than patients receiving epidural analgesia [37].

Abdominal pressure and oesophageal pressure

Current study has been demonstrated that protective ventilation during mechanical ventilation yield beneficial effect in terms of reduction of PPCs. In postoperative intraabdominal surgery or obesity, a decrease compliance results from an increase in chest wall elastance. In obesity, an increase in BMI has a negative correlation with lung volume and lung compliance during anaesthesia. Furthermore, increasing of Intraabdominal Pressure (IAP) correlates to increasing of chest wall elastance. Severe obesity patients with mechanical ventilation are more likely to develop ARDS than normal weight patients. In these cases, the airway pressure does not reflect the real stress and strain of lung tissue.

We recommend to pay more attention in measuring chest wall elastance, transpulmonary pressure and IAP especially in high risk postoperative abdominal surgery and obesity patients for optimising tidal volume and PEEP [38–40].

Regarding an availability of ultrasound, it is a totally non-invasive tool at bedside. The efficacy of lung ultrasound (LUS) is early detection of pneumothorax during perioperative period [41]. Furthermore, the characteristics of atelectasis, different from pneumonia due to the absence of dynamic air bronchogram is another usefulness of LUS as well as detecting the increasing of number and density of B-line representing extravascular lung water [42, 43].

Because LUS can rapidly detect PPCs thus it plays an important role for perioperative monitoring leading to early appropriate treatment.

8.4.3 Fluid Management in Perioperative Period

The recent study of fluid management in ARDS has demonstrated benefits of restrictive fluid management compare to liberal fluid management in terms of improvement of lung function and shortening duration of mechanical ventilation. However, in the patients undergoing surgery who are at risk for developing PPCs, fluid strategy showed different outcomes.

The liberal fluid therapy in knee arthroplasty and laparoscopic cholecystectomy has improved postoperative lung function and decreased vomiting symptom. On the contrary, restrictive fluid administration in abdominal surgery results in significant improvement of lung function and postoperative oxygenation [44]. Likewise, in major high risk surgery, that fluid therapy has been guided by continuous minimally invasive SV and oxygen delivery index, restrictive fluid strategy lead to decrease of postoperative major complications. However, among these complications the incidence of PPCs is comparable [45]. Recently, by retrospective analysis, the development of postoperative ARDS is associated with perioperative crystalloid and erythrocyte transfusion [46]. On the other hand, restrictive fluid management in major abdominal surgery associates with increase rate of postoperative ARDS [47].

In summary, current data about perioperative fluid management remain controversial between liberal versus restrictive strategies in terms of prevention PPCs. The inconsistent results vary to types of surgery and perioperative monitoring goal directed treatment. Thus, we require a large multicentre RCT to clarify this issue.

8.4.4 Preoperative and Postoperative Physiotherapy

Regarding pathophysiology of PPCs, anaesthesia induces the reduction of FRC and diaphragmatic function especially at postoperative abdominal or thoracic surgery. The aims of physiotherapy are promotion of early immobilisation, maintaining adequate ventilation, enhancing removal of bronchial secretion, prevention or re-expansion of atelectasis, prevention of nosocomial pneumonia and facilitating patients to return to preoperative independent functional status.

Incentive spirometry, Breathing exercise and Preoperative physiotherapy

Although incentive spirometry(IS) is widespread used, several meta-analysis studies show no benefit of IS in pre and/or postoperative care for preventing PPCs in abdominal, cardiac and thoracic surgery [48]. In cardiac surgery, recent meta-analysis has shown that preoperative inspiratory muscle training in 856 elective cardiac surgeries reduces atelectasis, pneumonia and the length of hospital stay [49]. On the contrary, several prospective studies in thoracic surgery, preoperative physiotherapy shows no difference in outcome related to PPCs but improvement of exercise capacity and length of stay [50, 51].

Perioperative physiotherapy

Cardiac surgery

In elective cardiac surgery, preoperative inspiratory muscle training can reduce PPCs and length of hospital stay [52]. Likewise, diaphragmatic muscle training can improve respiratory muscle strength at postoperative cardiac surgery [53]. Postoperative manual hyperinflation and ventilator hyperinflation have demonstrated the improvement of oxygenation and lung compliance, however no difference is observed in terms of PPCs [54].

Abdominal surgery

The meta-analysis of breathing exercise excluding the use of IS in upper abdominal surgery has demonstrated the improvement of respiratory muscle strength however the incidence of PPCs remains the same [55]. In patients undergoing oesophagectomy, postoperative chest physiotherapy consisting of lung re-expansion and airway clearance shows the lower incidence of PPCs [56].

Thoracic surgery

Although, the incidence of PPCs after thoracic surgery is relatively high, but there are few RCTs of physiotherapy in thoracic surgery. Patients undergoing lung surgery, physiotherapy with or without incentive spirometry can reduce PPCs in lung surgery comparing to previous studies [57]. However, no clearly evidence supports these results by RCT. Several studies try to use positive expiratory pressure therapy and flutter device, however no study shows difference in PPCs outcome [58].

Obviously, perioperative physiotherapy in cardiac and abdominal surgery could reduce PPCs, however in thoracic surgery we need the large RCT to confirm its benefits.

8.4.5 Non-invasive Ventilation During Perioperative Period

Patients who developed PPCs are at risk of re-intubation lead to prolong hospitalisation and increase of mortality. Applying of non-invasive ventilation (NIV) physiologically could improve oxygenation, recruit atelectasis and might improve mortality. Several studies demonstrated benefit of NIV in various types of surgery, time to initiation of NIV and outcome.

Pre-induction and after-induction continuous positive airway pressure

Since physiologic and evidence-base support that with pre-oxygenation might cause absorptive atelectasis. In morbid obesity, apply continuous positive airway pressure(CPAP) of 10 cmH_2O during and after induction could prevent atelectasis demonstrated by CT, associated with a better oxygenation [59] and increase non hypoxic apnoea duration [60].

Prophylaxis non-invasive ventilation following surgery

Following vascular and general surgery

Bagan el al randomised applying CPAP preoperative and postoperative in major aortic surgery. The authors demonstrated fewer PPCs and shorter duration of

hospital stay [61]. However the other studies did not show favourable outcome in intermittent postoperative NIV following general surgery.

Following Bariatric surgery and general surgery in obesity

In morbid obesity with obstructive sleep apnea (OSA) undergoing bariatric surgery, Neligan et al. prescribed pre-induction CPAP, intraoperative CPAP plus recruitment manoeuvre and postoperative Boussignac system at least 8 h. They demonstrated less reduction of all lung function measurement in intervention group [62]. Moreover, though using Boussignac system only after post-extubation until 2 h showed the improvement of PaO_2/FIO_2 ratio [63].

Following thoracic surgery

Perrin et al. randomised applying combined preoperative and postoperative NIV in pulmonary lobectomy patients compared with standard treatment. They demonstrated improved oxygenation and lung function as well as shorter hospital stay but not different in atelectasis [64]. Recent study by Liao et al. demonstrated few number of poor re-expansion of the lung after post thoracic surgery even using postoperative intermittent NIV furthermore show no difference pleural air leak between two groups [65].

Several studies using postoperative CPAP after thoracic surgery showed fewer PPCs [66].

Following cardiac surgery

Applying of NIV and CPAP in cardiogenic pulmonary oedema shows strong evidence reducing mortalities [67]. In large prospective RCT of 500 patients undergoing cardiac surgery prophylaxis CPAP of 10 cmH2O after extubation. PPCs, re-intubation and readmission rate to ICU are significantly reduced in CPAP group [68].

NIV for treatment postoperative respiratory failure

In the patients developed PPCs leads to re-intubation or prolong hospital or even mortality. In Japanese retrospective study showed improved oxygenation, decrease of respiratory cause mortality and re-intubation rate in post liver resection complicated respiratory failure [69]. Furthermore, this same positive result were demonstrated in patients follow lung resection [70] and solid organ transplantation [71]. This beneficial effect is decreasing if delayed NIV and associated with worse mortality [72].

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Old and New Strategies on Artificial Ventilation in ARDS Patients

9

Paolo Pelosi, Maria Vargas and Iole Brunetti

American-European Consensus Conference (AECC) made current definition of Acute respiratory distress syndrome (ARDS) in 1994. According to AECC, ARDS was defined by an acute onset of hypoxemia (PaO_2/FiO_2 ratio <200 mm Hg) and diffuse radiologic infiltrates in the absence of left atrial pressure.

During the years, the way to ventilate ARDS patients is deeply changed thanks to an increased knowledge of its pathophysiology. In this chapter, we report the main changes in the field of mechanical ventilation in ARDS patients.

ARDS is not a new disease; it is know since 1821 as "Idiopathic anasarca of the lung" [1]. Ashbough et al., made the first modern description of ARDS in 1967, while AECC made current definition of it in 1994 [1]. According to AECC ARDS was defined by an acute onset of hypoxemia (PaO_2/FiO_2 ratio < 200 mm Hg) and diffuse radiologic infiltrates in the absence of left atrial pressure [1].

During these 40 years the way we treat ARDS has truly changed. At the beginning, this disease was treated using mechanical ventilation obtained from

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anesthesiological and not from intensive care clinical practice. Actually, ARDS is well-known pathology but still a challenge for the intensive care physician.

As follow we report the main changes in the field of mechanical ventilation in ARDS patients.

9.1 Old Strategies on Artificial Ventilation in ARDS Patients

9.1.1 Tidal Volume

The mechanical ventilation approaches for patients with ARDS over the decades of the 1970s, 1980s, and early 1990s aimed to improve oxygenation and to normalize arterial carbon dioxide levels [2].

In those years, the recommended strategies to achieve these targets included the use of high tidal volume of 10–15 ml/kg actual body weight [2]. These levels of tidal volume seemed to be useful and safe for patients with normal lung parenchyma after major abdominal surgery but not so safe for lung injured patients. Just in that period, the first animal studies about the use of high tidal volume in mechanical ventilation provided an evidence of a severe lung damage produced by this ventilation strategy, probably due to the disruption of pulmonary endothelium and epithelium and the release of inflammatory mediators [3]. Later research demonstrated that the so-called *volotrauma* may worsen the lung damage in ARDS patients as a result of excessive distension or stretch of the aerated lung. In the 1986 Gattinoni et al., evaluated the distribution of lung aerated and non-aerated regions in patients with ARDS [4]. Interesting results of this study demonstrated an inhomogeneous distribution of aerated lung regions with normal compliance and non-aerated lung regions with a significantly reduced compliance [4]. So according to this study, the single areas of the same lung didn't have the same conduct regard lung injury. Gattinoni et al., in further studies also demonstrated that the lung aerated regions in ARDS patient were similar to a lung of a healthy child, so they called this small aerated lung parenchyma as *baby lung* [5].

The concept of baby lung had a key role in the comprehension and treatment of ARDS. In the 1990s years, according to this concept many clinical studies started to use a small tidal volume in mechanical ventilation of ARDS. In this period Hinckling et al., gained favor regards their animal study about small tidal volume versus large tidal volume in ARDS animals [6] and following human studies confirmed this topic. Brochard et al., evaluated the effect of low tidal volume (treatment group) versus high tidal volume (conventional group) in severe ARDS patients [7]. In the treatment group, the tidal volume was maintained between 6 and 10 ml/kg of actual body weight (IBW), while plateau pressure below 25/30 cm H_2O; in conventional group tidal volume was set above 10 ml/kg IBW. In this study, the author failed to find a favorable outcome in any of exanimated variables [7]. Amato et al., evaluated the effect of protective mechanical ventilation on mortality in ARDS patients [8]. In this study, the tidal volume was set on

12 ml/kg IBW in conventional ventilation and 6 ml/kg IBW with a peak airway pressure between 20 and 40 cm H_2O. This author found that a protective approach in mechanical ventilation improved the survival rate at 28 days and the weaning rate but not improved the hospital discharge [8].

Low tidal volume strategy in mechanical ventilation of ARDS patients may result in an increase of arterial carbon dioxide levels, called *permissive hypercapnia.* This event may have potentially harmful consequences as cerebral vasodilation, pulmonary vasoconstriction, and pulmonary hypertension. Experimental data suggested that permissive hypercapnia was not an adverse event but it was safe and potentially beneficial in this disease [9].

9.1.2 Positive End Expiratory Pressure

The use of positive end expiratory pressure (PEEP) during mechanical ventilation may improve oxygenation in ARDS patients. This effect was due to the PEEP prevention of the collapse of alveoli and small airway lacking of surfactant [2]. Further, keeping the alveoli open throughout the respiratory cycle, PEEP may prevent the damage produced by the repetitive opening and closing of the small airway and alveoli. PEEP levels used in clinical practice for ARDS patients were wide. Some studies in the 1990's years sustained that the adequate PEEP level for ARDS patients could be chosen by the analysis of pressure–volume curve [10]. During ARDS the pressure–volume curve assumed a particular sigmoidal shaped with two inflection points. According to the sigmoidal curve, the PEEP level at which recruitment of collapsed alveoli began, could be set between the lower and the upper inflection point [11]. Rupie et al., evaluated the static pressure–volume curve in ARDS patients [11]. They demonstrated in patient with severe ARDS the lower and the upper inflection point of sigmoidal compliance curve occurring at approximately 10 and 30 cm H_2O of inspiratory plateau pressure. At times, the ideal PEEP level to set in mechanical ventilation of ARDS patients could be chosen according to the lower inflection point, in contrast with the previous study of Ashbough et al., in which PEEP levels didn't exceed 5–10 cm H_2O [12].

9.1.3 ARDS Clinical Trials Network

ARDS clinical trial network was established in 1994 with the aim to test treatment strategies to improve the care of patients with ARDS using multi-center clinical trials.

After the study of Amato and Brochard, the first clinical trials of ARDS-network aimed to clarify the role of the low tidal volume on some important clinical outcome in this disease [13]. This multi-center clinical trial recruited 861 patients from 1996 to 1999 in 10 University intensive care department. 429 patients received traditional tidal volume set as 12 ml/kg of predicted body weight.

This volume was subsequently reduced stepwise by 1 ml/kg in order to achieve an inspiration plateau pressure less than 50 cm H_2O. 432 patients received the lower tidal volume set as 6 ml/kg of predicted body weight and subsequently adjusted to maintain the inspiratory plateau pressure less than 30 cm H_2O. The use of the lower tidal volume strategy was found to be efficacious in the reduction of mortality. Mortality was reduced of 22 % and also the number of ventilator free days was greater in lower tidal volume group.

In 2004 the ARDS-network published another clinical trial with the aim to investigate the role of higher PEEP levels on clinical outcome in ARDS patients receiving mechanical ventilation with lower tidal volume [14]. This clinical trial, conducted from 1999 to 2002 in 23 hospitals of the National Heart, Lung and Blood Institute (NHLBI), recruited 549 patients. 273 patients received mechanical with lower PEEP level (8.9 ± 3.5 in day 1, 8.5 ± 3.7 in day 3, 8.4 ± 4.3 in day 7), while 276 patients received the higher PEEP level (14.7 ± 3.5 in day 1, 12.9 ± 4.5 in day 3, 12.9 ± 4.0 in day 7). As results of this study, there were no significant differences in mortality, in ventilator free days or organ failure between lower and higher PEEP groups [14].

Checkley et al., in 2008 evaluated the effects of ARDS-network clinical trial on mechanical ventilation practise in ARDS patients [15]. In ARDSnet hospital tidal volume was 10.3 ml/kg of predicted body weight (PBW) during the lower tidal volume trial, 7.3 ml/kg PBW at the end of this trial and 6.8 ml/kg PBW in 2005. Plateau pressure was 27.7 cm H_2O during lower tidal volume trial and 26.3 cm H_2O in 2005. The use of PEEP changed modestly from 1996 to 2005. PEEP increased from 8 cm H_2O in the lower tidal volume to 10 cm H_2O in 2005. This study demonstrated that in ARDS-network hospital physicians changed the setting of mechanical ventilation in ARDS patients. The changes adopted were most apparent in the management of tidal volume that was set to a lower level, but not in the management of PEEP levels that didn't changed significantly across the years.

9.2 New Strategies on Artificial Ventilation in ARDS Patients

Protective ventilator strategy based on lower tidal volume became the standard of care for ARDS patients in intensive care unit. Nevertheless, tidal volume level of 6 ml/kg seemed to be not appropriate for all ARDS patients [16]. Recently Gattinoni et al., stated that tidal volume adjusted for ideal body weight and airway pressure are surrogate of lung stress and strain and may be misleading in ARDS patients [17]. In fact, the protective mechanical ventilation was found harmful in a prospective randomized clinical study by Fanelli et al. [18]. In this study, the author found that low stretch/lung rest strategy, defined as TV of 6 ml/kg and PEEP of 8–10 cm H_2O, was associated to less apoptosis, which were protective against lung damage, and more ultrastructural evidence of cell damage [18]. In patients suffering from ARDS, mechanical ventilation is the life-treating therapy required to optimize gas exchange, to avoid and reduce work of breathing

preventing respiratory fatigue. For many years the use of controlled mechanical ventilation with protective setting and deep patients sedation and muscle paralysis was able to control lung stress and strain, but it may lead to a diaphragmatic dysfunction [19]. With this purpose in mind, the role of spontaneous breathing in ARDS patients has been more debated in the past years. Gama de Abreu et al., supported the use of spontaneous breathing in ALI/ARDS in a recent paper. In this work, the author used biphasic positive airway pressure with spontaneous breathing which is a combination of time-cycled controlled breaths at two levels of continuous positive airway pressure and non-assisted spontaneous breathing [20]. The author found that this ventilation increased the aeration of dependent zones, decreased tidal reparation and hyperaeration during spontaneous breathing, and produced a better oxygenation. Yoshida et al., evaluated the impact of spontaneous ventilation during airway pressure release ventilation (APRV) and pressure support ventilation (PSV) on distribution of lung aeration in patients with ARDS [21]. Pulmonary oxygenation was better during APRV than during PSV when delivered with the same mean airway pressure. While PSV didn't affect lung aeration, spontaneous breathing with APRV improved lung aeration decreasing the amount of collapsed tissue and improving pulmonary oxygenation. Spontaneous breathing activity during ARDS had potential disadvantages. This ventilation lack of a tidal volume control resulting in excessive lung stress and strain on damaged tissue responsible of an increase in proinflammatory response and than in mortality. The interaction between patient and ventilator may have different degrees of asychronization due to the common causes reported in spontaneous activity.

Recently a different model of spontaneous ventilation, involving a variation of breathing pattern, has been proposed in mechanical ventilation for ARDS patients. The variation of breathing pattern in terms of respiratory rate and tidal volume may improve the function of a damaged lung parenchyma. The concept of breathing pattern variation in ARDS/ALI was built on the observation that protective ventilation strategies had a monotonic pattern without any physiological variation of spontaneous breathing. According to this hypothesis, Spieth et al. evaluated the impact of variable tidal volume at fixed respiratory rate in a surfactant depletion model of lung injury [22]. Variable tidal volume was set in a mechanical ventilation previously established by ARDS-network and compared with this one without variability. The use of random variable tidal volume improved lung function and histological damage during mechanical ventilation without increasing lung inflammation and mechanical stress [22]. Variable tidal volume spontaneous ventilation is now known as noisy pressure support ventilation (noisy PSV). In this ventilation the variation of pressure support may lead to different degrees of variation in tidal volume. Spieth et al., in a recent study evaluated the effect of noisy-PSV on lung function in ALI/ARDS animals [23]. The target of pressure support represented the value needed to obtain a tidal volume of 6 ml/kg and the percentage of variability has been set around this value. Noisy-PSV improved the elastance of respiratory system, peak airway pressure, P/F ratio without increasing $PaCO_2$.

9.2.1 Positive End Expiratory Pressure

ARDS-network failed to show the best degree of PEEP to apply in mechanical ventilation for ARDS patients. General consensus exists about the use of PEEP in ARDS to keep open alveoli and small airway. Different high levels of PEEP have been shown to prevent and/or worsen lung damage in animal study. At the same time, random use of high PEEP levels didn't show a significant improvement of lung function in ARDS large human trials. In this scenario, the strategy of open lung approach was suggested with the aim to open recruitable alveoli and keep it open during respiratory cycles. In open lung PEEP strategy, the recruitment of alveoli is performed using recruitment maneuver with different PEEP level. Once the alveoli are open, they are kept open with a PEEP level that prevents their collapse. Recently, Gernouth et al., reported the use of computer-control open lung strategy on respiratory function and hemodynamic in ARDS patients [24]. The open lung procedure was divided into a lung recruitment phase and open lung PEEP titration. In recruitment phase, PEEP level was set to 20 cm H_2O and the lung was recruited with a stepwise increase of driving pressure up to 30 cm H_2O. Then, the alveoli were kept open using a decremental PEEP level by 2 cm H_2O, keeping driving pressure constant and recording dynamic compliance of respiratory system. This study showed that computer-control open lung strategy with recruitment maneuver followed by decremental PEEP trial, improved respiratory system mechanics and oxygenation in ARDS patients already ventilated with the protective strategy of lower tidal volume and higher PEEP.

Nevertheless, this computerized strategy didn't significantly compromise the hemodynamic in the same group of patients.

9.3 Conclusion

The well-known strategy of lower tidal volume and higher PEEP level, suggested by many trials including ARDS-network, for many years was the best mechanical ventilation to apply in ARDS patients. Actually, the huge technological progress in intensive care medicine allowed us to improve our knowledge in lung injury and offered us new and advanced solution to treat it in the best way possible.

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Minimally Invasive Thoracic Surgery

10

Marcello Migliore

10.1 Introduction

Although it is known that the first thoracoscopy has been performed by Jacobeous when he introduced the cystoscope to look inside the chest [1], the Viennese physician Josef Grünfeld reports in an article published in 1879 that, according to Samuel Gordon, Dr. Francis Richard Cruise "performed an endoscopic examination of a chest fistula using a binocular device that made his instrument more perfect" [2, 3].

In the last 20 years the minimization of the invasiveness of surgical procedures has been a rule in most thoracic surgical units worldwide, and with the advancements in video imaging, endoscope technology, and instrumentation it is now possible to convert many open surgeries to minimally invasive. In particular the use of minimally invasive approaches in thoracic surgery has changed the strategic approach to all surgeries. The pain, discomfort, and disability, or other morbidity as a result of surgery is more frequently due to trauma involved in gaining access to the area to perform the intended procedure rather than from the procedure itself.

There is a worldwide increase in the number of procedures performed using minimally invasive techniques. A shift has taken place in thoracic surgery, with a large portion of procedures now being performed through a video-assisted thoracoscopic surgery (VATS) approach.

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10.2 Definition

Although it is known that the era of Minimally Invasive Thoracic Surgery (MITS) initiated 100 years ago, the abbreviation and terminology used to indicate the right mini-invasive approach are not used homogeneously; in fact, some authors use thoracoscopic surgery, others video-thoracoscopy, and others video-assisted thoracic surgery (VATS). In few words are worldwide surgeons talking the same language? For example is VATS lobectomy a key-hole surgery? What does it mean single port or single trocar VATS technique?

We have previously attempted to classify the term VATS, which should be used in the medical literature when the standard thoracoscope is not employed. In such cases the optic is separated from the surgical instrument and the chest tube is always positioned under video control. This can be achieved through a 2 cm single skin incision, a single flexible trocar, or by means of 2-3-4 trocars and finally using a mini-thoracotomy of 5–6 cm [4].

10.3 Indications

At present, all of surgeries shown in Table 10.1 can be performed by using mini-invasive thoracic technique in terms of the surgical technology. Nevertheless, the role of mini-invasive thoracic technique in treatment may be differential based on different diseases, different disease degrees, and surgeons' experience [5].

10.4 Techniques

Minimally invasive thoracic surgery can be performed using different techniques (Table 10.2). Single trocar and uniportal are not identical because the single trocar utilizes a flexible trocar, while the uniportal uses the single skin incision. Both

Table 10.1 Minimally invasive thoracic surgery procedures

• Lung	Wedge resection, lobectomy, bilobectomy, sleeve resection, pneumonectomy, bullectomy, lung volume reduction surgery
• Pleura	Pleural biopsy, empyema decortication, drainage of effusion, pleurodesis, pleurectomy (pneumothorax or mesothelioma)
• Diaphragm	Repair of eventration, plication of diaphragm, closure of pleuroperitoneal fistula
• Mediastinum	Thymectomy for myasthenia gravis, tumor excision (such as neurogenic tumor), ligation of thoracic duct, lymph node biopsy
• Esophagus	Fundoplication, myotomy, diverticulectomy, peroral myotomy, esophagectomy
• Pericardium	Pericardial window, excision of pericardial cyst
• Autonomic nervous system	Sympathectomy

Table 10.2 Minimally invasive thoracic surgery techniques

Single trocar
Uniportal
Two–three ports (triangle)
Hybrid
Using a mini-thoracotomy
Robotic

techniques are employed to perform simpler thoracic procedures (pleural and mediastinal biopsy, symphatectomy, pneumothorax). Three ports are used for more complex procedures such as esophageal dissection during VATS esophagectomy. A mini-thoracotomy is essential in major lung resection because the necessity to remove the lobe; therefore, it is always safer to perform the incision at the beginning of the operation. Moreover, conventional instruments can be employed. The hybrid method is used to perform extracorporeal lung biopsy or to palpate mediastinal nodules during mediastinotomy. The concept of robotics in surgery involved operating at a site remote from the surgeon. Although simple surgical procedures have been performed remotely, there are no clear guidelines to practical application at present because of expense, transmission delay, and medical and legal issues. It is obvious that multicenter trials or comparably rigorous nonrandomized evaluations are needed to determine which patients benefit from open surgical approaches and which from robot-assisted approaches [6]. Nevertheless, robotics is impacting the field of minimally invasive surgery.

10.5 Anesthesia and Perioperative Management

In general all VATS procedures represent an indication for one-lung ventilation and the perioperative principles of management, including antibiotic treatment, are similar to those during pulmonary resection [7]. In some circumstances sedation and local or regional anesthesia or general anesthesia with double-lung ventilation can be used.

The simplest technique is to use a local anesthetic to infiltrate the lateral thoracic wall and parietal pleura. Alternatively, intercostal nerve blocks can be performed at the level of the incision(s) and at two interspaces above and below. For VATS procedures under local or regional anesthesia, to anesthetize the visceral pleura, topical local anesthetic agents can be applied. Intravenous sedation with propofol may be needed to supplement the regional nerve blocks. The major disadvantage of VATS under local or regional anesthesia is that because the patient breaths spontaneously the lung can fill the cavity, and the surgeon doesn't have enough space to work. This is usually tolerated for short periods of time, but for most VATS procedures a general anesthetic with controlled one-lung ventilation is a better choice. There are two main methods for lung isolation: Use of a double-lumen endobronchial tube or insertion of an endobronchial blocker.

Feasibility study of a novel double-lumen endotracheal tube and bronchial blocker has been tested in human cadavers [8].

Planning postoperative pain management begins during the preoperative evaluation, and implementation generally occurs during anesthesia. Because minimally invasive surgery is reported to be less painful, epidural analgesia is generally not employed. The surgeon can infiltrate the trocar insertion sites with the long-acting local anesthetics bupivacaine or ropivacaine, and opioids or nonsteroidal anti-inflammatory agents can be administered postoperatively as indicated. Prophylactic use of noninvasive positive pressure ventilation after video-assisted thoracoscopic surgery has been proved to be beneficial [9].

It is important to advice the patient because expectations are very high and minimal invasive approach is often falsely associated with minimal risk. Perioperative patient management which is consisted of the cooperation between the surgeon and the anesthetist, correct preoperative evaluation, preoperative medical treatment with pulmonary rehabilitation, appropriate anesthetic management, and postoperative intensive care are mandatory in a modern hospital to achieve excellence in thoracic surgery.

10.6 Diseases of Pleura and Chest Wall

VATS technique has been commonly employed in the pleura disease, and the most common procedure are pleural biopsy, pleural decortication, and pleurodesis, or clearance of effusion, empyema and haemothorax, ligation of fractured intercostal arteries, or ruptured thoracic ducts. To treat simple diseases of the pleura a single trocar or a uniportal VATS technique is generally sufficient. General anesthesia is not mandatory, and local anesthesia can also be used [10–12]. Talc pleurodesis for malignant pleural effusion is easily performed using a single trocar VATS technique with a success rate between 90 and 100 %, and similar results [13] have been reported in 28 patients with stage II empyema with 100 % success [12].

Most surgeons now perform the Nuss surgery to treat funnel chest by hanging up the sternum after placing arcuate buttress plate on the back of sternum, which was a major advance in treatment of funnel chest. These surgeries are uncomplex in technique and low-risk. Thoracic surgery can minimize trauma and greatly improve the accuracy of surgeries, which is thus fit for application [14].

In the modern era, the well-known method of pleuro-pneumonectomy to treat mesothelioma is under discussion in view of the absence of benefit for the patients and high morbidity [15], therefore an interest is born regarding the radical VATS pleurectomy/decortication with hypertermic intraoperative chemotherapy which might offer an alternative treatment option [16]. About 55 out of 63 patients were highly satisfied with the result of endoscopic sympathectomy, which is considered the appropriate minor procedure for the treatment of upper limb hyperhidrosis, causing minimal discomfort to the patient and almost invisible scars [17].

10.7 Diseases of the Lung

The surgical procedures performed on the lung via a minimally invasive approach are bullectomy, wedge resection, lung volume reduction, lobectomy, pneumonectomy, and bronchoplasty surgery. Lung wedge and lung anatomical resections remove a fraction of lung tissue from patients for diagnosis and treatment. Lung biopsy is the last option in order to obtain lung tissue for a precise diagnosis in patients with diffuse lung disease, and lobectomy or pneumonectomy are generally used to treat lung cancer.

Bullectomy and lobectomy are generally performed using the three ports method but recently few authors use one port [18] and some other prefer an awake approach in a subgroup of patients with suffering of pneumothorax [19]. Pleurodesis is performed using pleurectomy or abrasion with sponge, and few others use talc.

Several techniques have been reported to perform lung biopsies. Since the introduction of minimally invasive technique, most authors prefer the classic three ports VATS approach and few favor the uniportal method [17], many surgeons still use the standard open approach which is the preferred option in patient who unable to tolerate single lung ventilation.

In patient with intraparenchymal solitary pulmonary nodule VATS has the major disadvantages that it is not possible to palpate the lung, therefore several methods have been developed to locate the nodule such as methylene blue injection and insertion of a guidewire into the lung nodule, intraoperative ultrasound, CT-guided hookwire localization. When there is the suspicious of a lung metastasis it is important to have the main tumor under control and an accurate palpation of the entire lung must be performed to detect more nodules. In every case it is absolutely necessary to try to avoid a pneumonectomy because the high risk associated with this procedure [20].

In patients with diffuse lung diseases we have recently developed a hybrid VATS through a single trocar to biopsy the lingula [21]. The telescope permits one to identify and deliver the lingula outside the chest, where it is resected. The operation permits a safe collection and adequate histopathologic sample, and it takes a total of approximately 10 min. The main innovative aspects of this technique are (a) less trauma to the patients because there is no rib spreading as in the open method; (b) it avoids crowding of surgical instrumentation in the operative field as in the uniportal method; (c) the operation can be performed without lung collapse; (d) it avoids the 5–8 cm mini-thoracotomy in patients who cannot tolerate single lung ventilation; (e) the operation can be performed on the bed side in intensive care unit.

(a) Lung cancer

At the beginning, the first reports of VATS technique to perform lobectomy to treat lung cancer created a long controversy and suspicion because the lack of accurate lymph node dissection. Nowadays, it has been clearly demonstrated that mortality is below 1 % with a complication rate of 10 % and length of stay with a

median of 3 days. The conversion rate is 2.5 % and air leak and atrial fibrillation are the commonest complications. A 5 year survival rate is similar to open surgery [22–24], and an effective lymph node dissection have been demonstrated [25, 26]. More studies have shed light on other advantages of VATS such as alleviated pain after surgery, minimal blood loss during surgery, more favorable pulmonary function after surgery, and less cytokine responses compared with conventional surgery [27].

Thoracic surgeons with the increase of surgical practice are now more prone to perform VATS resection and dismissed many worries [28]. Thus, VATS radical resection of pulmonary carcinoma was identified and believed to be included in the standard treatment approach of resection of pulmonary carcinoma by National Comprehensive Cancer Network (NCCN) guideline, which is also greatly suggested for old people and people with poorer constitution [29]. In recent years, along with the development of mini-invasive thoracic technique and an update of conception, mini-invasive thoracic surgery can be performed not only on patients with stage I or stage II lung cancer [24, 25], but also in patients with stage III lung cancer [30].

10.8 Mediastinal Diseases

In the mediastinum mini-invasive surgery permits to remove the thymus gland for non-thymomatus mediastinal myasthenia gravis, ectopic thyroid gland, thymic cyst, and stage I thymoma [31]. Video-assisted transcervical thymectomy which is an improvement of the standard trancervical thymectomy [32], and experience with the "da Vinci" robotic system for thymectomy in patients with myasthenia gravis have been proved beneficial [33, 34]. The results of video-assisted transcervical thymectomy in the treatment of myasthenia gravis are similar to open technique therefore it is obvious nowadays to prefer the less invasive technique.

Video mediastinoscopy is performed by inserting the video instrumentation in the mediastinum to diagnose and remove the pathological tissues or swelled N2 or N3 lymph nodes to stage lung cancer. The concept of video mediastinoscopy was presented by the Leuven group already in 1993 at the First International symposium on thoracoscopic surgery in San Antonio January 22, 1993 [35]. The visual advantages are clearly demonstrated in Fig. 10.1.

Video techniques can also be used in case of massive mediastinal goiter or during anterior mediastinotomy to enhance the operation [36, 37].

10.9 Esophageal Diseases

Video-assisted thoracoscopy and laparoscopy permit nowadays to perform appropriate treatment of almost all esophageal diseases. Thoracic surgeons with interest in esophageal disease perform laparoscopic repair of hiatal hernia and gastroesophageal reflux. Long-term results have been demonstrated are the same

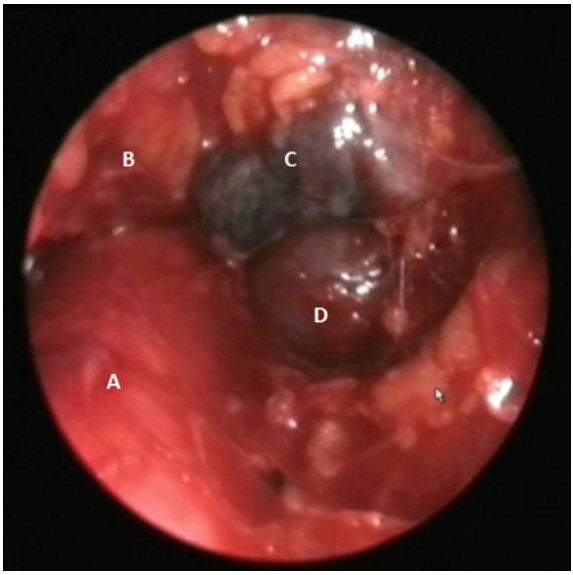

Fig. 10.1 Intraoperative view of a video mediastinoscopy. *a* right main bronchus *b* right pulmonary artery *c* R4 node *d* azygos vein

of laparoscopic surgeons [38]. Complications raised in the last decennium because of the large number of operated patients, but nowadays the indications for the operation are reduced and the number of complications is therefore decreasing [39]. The belsey mark IV fundoplication is used only in rare circumstances [40].

Heller myotomy on thoracoscope has been considered as a safe and effective approach in the treatment of esophageal achalasia, and VATS resection of benign esophageal neoplasm or esophageal diverticulum is also convenient and simple, which is thus commonly performed. Peroral endoscopic myotomy (POEM) has been developed in the context of natural orifice transluminal endoscopic surgery (NOTES) as a minimally invasive endoscopic treatment for symptomatic esophageal achalasia [41]. Results are encouraging and there some centers are performing several prospective studies. Endoluminal surgery perhaps can be in the future also a good tool to remove endoluminal growth esophageal tumors such as fibroma or fibrolipoma [42, 43]. There is still a debate regarding the best treatment for Zenker Diverticulum [44]. The preferred option to treat Zenker diverticula larger than 3 cm treated is the use of transoral endoscopic stapler. A recent retrospective study on 107 patients who were treated endoscopically by CO_2 laser or staple-assisted diverticulostomy showed that patients in the staple-assisted group had a shorter duration of postoperative hospitalization, attributed to earlier oral intake, than patients in the CO_2 laser group. The authors concluded that the staple-assisted method seemed to be the most favorable [45].

Nevertheless, there are still debates over mini-invasive technique in treatment of malignant esophageal diseases. At present, along with the development of more than 10 years, mini-invasive esophagectomy (MIE) can favorably decrease the occurrences of complications and the recovery time after surgery as compared with

the conventional surgery and mini-invasive surgery is suitable for the old patients with esophageal cancer [46]. It is clear that surgical experience is important [47]. Indication for MIE includes patients with stage I and II, while patients with airways invasion cannot be treated at this moment with minimally invasive technique [48]. Thoracoscope-assisted transthoracic esophagectomy (TATTE) and mediastinoscope-assisted transhiatal esophagectomy (MATHE) are two types of MIE. Shorter operative time for MATHE (194.4 min) versus TATTE (228.1 min), less blood loss during operation in the TATTE group (142.6 ml) versus the MATHE group (214.6 ml), and more lymph nodes retrieved in the TATTE group (19.1 nodes) versus the MATHE group (11.4 nodes) have been demonstrated with no difference in survival between the groups [49].

A recent systematic literature search was performed using synonyms for minimally invasive or thoracoscopic esophagectomy, and 18 retrospective cohort studies and 3 meta-analyses were reviewed. The authors have demonstrated that total MIE using both the thoracoscopic and laparoscopic approach is increasingly performed. A longer operative time and less blood loss are observed with MIE in comparison to open esophagectomy (OE). Although the benefit of MIE for reducing morbidity and mortality rates is still under debate, a shorter hospital stay was common among the studies. The oncologic outcomes of MIE were not inferior to OE, while the number of retrieved lymph nodes was greater in MIE than OE in several studies. Although the benefits for short-term outcomes are still controversial, it seems that oncologic outcomes are favorable and MIE may have an advantage in lymph node dissection over OE [50]. It is evident on the basis of these reports that the benefits of MIE should therefore be confirmed by randomized controlled trials.

10.10 Future

Future research will focus on delivery of diagnostic and therapeutic modalities through natural orifices in which investigation is under remote control and navigation, so that truly “noninvasive” surgery will be a reality [51].

Other possible roles for computer and robotic assistance in surgery include transcontinental tele-robotic surgery [52], voice control over surgical manipulators, and information manipulators. Future developments will guarantee the possibility to insert additional data to the operative field, including 3-dimensional magnetic resonance imaging reconstructions and physiologic data acquisition.

Technologies that will impact surgery include the developments in the remote delivery of focused energy under image guidance will permit the ablation of tumors of the lung without the need for an incision. Noninvasive approaches may potentially be used for ablating plaques in arteries, revascularizing the myocardium. Advancements in microchip and wireless technology may allow the development of swallowable micro-robots for precise surgical procedures. Looking the present, the future of minimally invasive thoracic surgery for the benefit of our patients appears bright because the potential of technology is enormous.

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Part VI
Severe Infections, Sepsis and MODS

Diagnosis of Ventilator-Associated Pneumonia

11

Luciano Silvestri, Hendrick K. F. van Saene and Serena Tomasino

11.1 Introduction

Ventilator-associated pneumonia (VAP) is the most frequent severe infection in the intensive care unit (ICU) affecting about 20–30 % of mechanically ventilated patients [1–3]. The risk of developing VAP is about 3 % per day for the first 5 days of ventilation, 2 % per day for days 6–10, and subsequently 1 % per day [4]. VAP is associated with increased morbidity, such as prolonged stay in the ICU, prolonged duration of mechanical ventilation, and increased costs. Crude mortality ranges from 20 to 50 %; attributable mortality of VAP is approximately 10–13 % [5, 6].

Diagnosis of VAP is difficult. Several criteria have been proposed including radiological techniques, clinical manifestations, and various methods of sampling of bronchoalveolar specimens. The aim of this chapter is to discuss radiological, clinical, and microbiological criteria for the diagnosis of VAP.

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11.2 Clinical Diagnosis

Chest X-ray is commonly used to diagnose VAP. However, a variety of conditions, such as segmental or lobar atelectasia, adult respiratory distress syndrome, alveolar hemorrhage, lung infarction, or congestive heart failure, may be erroneously interpreted as pneumonia. This may create a potential for overdiagnosis of VAP. There are no specific radiographic signs which may well correlate with pneumonia [7]. Chest X-ray is sensitive (78 %), but not specific (42 %) for the diagnosis of pneumonia when compared with histopathology of post-mortem lung biopsy [8].

Clinical signs, such as fever and leucocytosis, have intermediate predictive values [9], and they have been associated to radiological findings of the lung to diagnose VAP.

Forty-one years ago, Johanson et al. proposed a combination of criteria to diagnose VAP (Table 11.1) [10]. They included a new or progressive infiltrate on chest X-ray, plus at least two of the following conditions: fever >38 °C, leucocytosis or leucopenia, and purulent tracheobronchial secretions. However, if this set was compared to immediate post-mortem lung biopsies, the sensitivity and specificity were 69 and 75 %, respectively [10]. Despite the relative low accuracy of these criteria, they are recommended by influential authorities and scientific societies [1, 3].

In 1991, Pugin et al. introduced the clinical pulmonary infection score (CPIS), based on six variables including fever, leucocytosis, tracheal aspirate, oxygenation, chest X-ray findings, and cultures of the tracheal aspirate with Gram staining (Table 11.1) [11]. Initially CPIS showed a high performance (sensitivity of 93 % and specificity of 100 %). Subsequent studies demonstrated a sensitivity of 72 % and a specificity of 42 % if compared to histopathological diagnosis [9], and a sensitivity of 30–89 % and a specificity of 17–80 % if compared with bronchoalveolar lavage (BAL) [12]. However, an important limitation of the validation of CPIS for diagnosis of VAP is the lack of a "true" gold standard as comparator. In addition, the calculation of CPIS has been modified by some authors who also found a poor interobserver agreement [13].

Finally, the Centers of Disease Control and Prevention (CDC) proposed a definition including radiological, clinical signs, and microbiological features (Table 11.1) [14].

As clinical criteria have an intermediate predictive value they should be used in combination with radiological and microbiological findings in diagnosing VAP.

In 2013, the CDC has proposed a "surveillance" definition in order to limit the inaccuracy of VAP definition, and to improve the reproducibility of the diagnosis [15]. The aim of this new definition, i.e., ventilator-associated event (VAE), is only for public reporting and interfacility comparisons, and it should not be used for patients' care. The most important differences of this approach are the detection of all VAEs, not only VAP, the choice of only objectively recordable data, rigid time thresholds, and the omission of radiological findings due to their unreliability.

Table 11.1 Clinical signs for the diagnosis of ventilator-associated pneumonia

Johanson criteria [10]	New or progressive pulmonary infiltrate, plus:
	At least 2 of the following:
	- Fever >38 °C
	- Leucocytosis or leucopenia
	- Purulent secretions
Clinical Pulmonary Infection Score (CPIS) [11][a]	Temperature (°C): 36.5–38.4 = 0 point
	38.5–38.9 = 1 point
	<36.5 or ≥39 = 2 points
	Blood leukocytes (cells/mL): 4.000–11.000 = 0 point
	<4.000 or >11.000 = 1 point
	≥50 % bands = 2 points
	Oxygenation (PaO_2/FiO_2): > 240 or ARDS = 0 point
	≤240 or no ARDS = 2 points
	Chest X-ray: no infiltrate = 0 point
	Progressive infiltrate = 2 points
	Tracheal secretions: absence = 0 point
	Non-purulent = 1 point
	Purulent = 2 points
	Endotracheal aspirate: minimal or no growth = 0 point
	Moderate or heavy growth = 1 point
	Same bacteria seen on Gram stain = add 1 point
Centers for Disease Control and Prevention (CDC) [14]	Two or more serial chest radiographs with at least one of the following:
	- New or progressive infiltrate
	- Consolidation
	- Cavitation
	At least one of the following signs or symptoms:
	- Fever (>38 °C)
	- Leucopenia (<4,000 white blood cells/mL) or leucocytosis (≥12,000 white blood cells/mL)
	- Altered mental status, if age >70 years
	At least two of the following

(continued)

Table 11.1 (continued)

	- New or worsening cough, dyspnea, tachypnea
	- Rales
	- Worsening gas exchange
	Microbiology. At least one of the following:
	- Positive quantitative culture from minimally contaminated lower respiratory tract specimen. Specimen obtained via endotracheal suctioning is not a minimally contaminated specimen and therefore does not meet the laboratory criteria
	- Positive culture of pleural fluid
	- Positive culture on lung tissue histological exam
	- Positive growth in blood culture not related to another source of infection

[a] Total score >6 is consistent with ventilator-associated pneumonia; *ARDS* adult respiratory distress syndrome

11.3 Role of Microbiology in Improving the Accuracy of Clinical Diagnosis

Several microbiological techniques and methods of sampling of the lower airway secretions have been used for diagnosing VAP. Clinicians may obtain samples form the lower airways using non invasive methods, such as tracheal aspirate (TA), and invasive methods such as bronchoscopic or non-bronchoscopic guided BAL, or protected specimen brush (PSB). Additionally, each type of sample can be analyzed both qualitatively and using a quantitative (or semiquantitative) method. The cut-offs for quantitative methods are 10^4 colonies forming units (CFU) for BAL and protected BAL, 10^3 CFU for PSB, and 10^5 CFU for TA [16].

The American Thoracic Society/Infectious Diseases Society of America and the CDC advocated the use of invasive techniques of sampling and quantitative analysis to confirm VAP and to distinguish colonizing microorganisms from causative pathogens [1, 15]. Noninvasive techniques are sensitive but low specific, while invasive methods seem to be more specific for the diagnosis of VAP [17, 18]. Therefore, various invasive methods are used aiming at identifying the causative microorganisms and trying to distinguish colonization from infection. However, there are no conclusive data on which technique is superior to another. Additionally, quantitative cultures obtained by different methods of sampling seem to be quite equivalent for the diagnosis of VAP. Compared with pathologically confirmed diagnosis of VAP, BAL has a sensitivity of 19–83 % and a specificity of 45–100 %, PSB has a sensitivity of 3–83 % and a specificity of 66–100 %, and TA a sensitivity of 44–87 % and specificity of 31–92 % [13].

A Cochrane meta-analysis evaluated whether quantitative cultures of respiratory secretions were effective in reducing mortality compared with qualitative cultures [19]. The studies that compared quantitative and qualitative cultures (1,240 patients) showed no statistically significant differences in mortality rates (risk ratio [RR] 0.91; 95 % confidence interval [CI] 0.75–1.11). Duration of mechanical ventilation, length of ICU stay and antibiotic change were not significantly different between the interventions.

A Canadian randomized trial compared BAL with quantitative culture with TA with nonquantitative culture of the aspirate. The study demonstrated that there was no significant difference in the 28-day mortality rate between the two groups, and that the two groups had similar morbidity outcomes, such as organ dysfunction scores, length of ICU and hospital stay, days without antibiotics [20]. These observations have been confirmed by the Cochrane meta-analysis showing no evidence of reduction in mortality in the invasive group versus the noninvasive group (RR 0.93; 95 % CI 0.78–1.11) [18], and are consistent with the results of three Spanish trials [21–23].

Interestingly, a survey performed in European ICUs reported that invasive diagnostic tools were used in only 39 % of patients with VAP, BAL accounted for 13.6 %, PBS for 5.8 %, and blind techniques for 19.6 % of the cases [24].

Therefore, there is no a robust evidence that the use of quantitative cultures of respiratory secretions may decrease mortality and morbidity of VAP. Similar results are observed when invasive strategies are compared with noninvasive strategies.

Several studies investigated the value of Gram stain in the diagnosis of VAP. The results of these studies are contradictory [25]. The presence of bacteria in Gram stains of BAL has a sensitivity of 44–90 % and a specificity of 49–100 % in identifying patients with VAP [13]. A post hoc analysis of a multicenter Canadian randomized trial [25] demonstrated that TA and BAL Gram stains poorly predicted antibiotic treatment required according to the final culture results.

The presence of intracellular microorganisms in inflammatory cell (i.e., leukocytes) has been also proposed. The presence of 2 % intracellular microorganisms has a sensitivity of 75–86 %, and a specificity of 78–98 % in diagnosing the initial episode of VAP [12]. However, other authors investigated different cutoffs, such as 5 or 7 % and reported contradictory results [12].

Positive blood cultures in patients with VAP range from 8 to 20 %, with a sensitivity of 26 % [26].

Remarkably, a prior antibiotic therapy may influence the results of microbiologic cultures, the number of inflammatory cells, and the Gram-stain method [12, 27]. Therefore, secretions from the lower airways should be obtained before antibiotics, or new antibiotics, are administered.

Finally, a care bundle for VAP diagnosis has been developed by a European expert committee [28]. The three interventions for VAP diagnosis considered most appropriate were (a) early chest X-ray with expert interpretation, (b) immediate reporting of respiratory secretion with Gram stain including cells, and (c) quantitative microbiology before starting or changing treatment.

11.4 Conclusions

The diagnosis of VAP is a difficult task. Clinical criteria are helpful in the diagnosis of VAP. Microbiology does not increase the accuracy of clinical diagnosis. Quantitative cultures from TA, BAL, or PSB are quite equivalent for the diagnosis of VAP. Blood cultures are nonsensitive. Gram stain and cytological data may be influenced by prior antibiotic therapy. At the present, a diagnostic tool including clinical signs, chest radiograph, and microbiology of quantitative (or semiquantitative) sampling, either invasive or not, can be considered a reliable approach.

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Rationale of Antibiotics Anti-MRSA in Pneumonia

12

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Staphylococcus aureus is a bacterium causing a broad variety of infections, ranging from minor skin infections to severe pneumonia and sepsis. The genetic adaptation occurred after the introduction of meticillin into clinical practice in the 1960s [1] has led to a multidrug-resistant pathogen, methicillin-resistant *S. aureus* (MRSA). MRSA is characterized by the mecA gene that encode the penicillin binding protein 2a (PBP2a) that permits growth in the presence of meticillin and tends to have multidrug resistance. MRSA is resistant to b-lactam antibiotics, including penicillin and cephalosporins but not ceftaroline that is able to bind PBP2a.

S. aureus was considered in the past as an important but infrequent cause of nosocomial pneumonia, occurring especially in elderly patients [2].

However, in recent years there has been a dramatic increase in pneumonia caused by MRSA accounting for 20–40 % of all hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Recently, most of the MRSA strains causing health care-associated pneumonia (HCAP), HAP, and VAP were labeled hospital-acquired MRSA (HA-MRSA) [3]. Recently, a new variant of MRSA has emerged as a pulmonary pathogen. This new variant of *S. aureus* that causes pneumonia is community-acquired MRSA (CA-MRSA), containing SCC-mec type IV [4].

Overall, MRSA is an important cause of pneumonia and was identified by a number of logistic regression analysis as the only pathogen independently associated with mortality [5].

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12.1 Therapy

For years, vancomycin and teicoplanin were the only antibiotics available for the treatment of MRSA pneumonia. However, the cure rate was not satisfactory [6, 7]. MRSA pneumonia and methicillin-susceptible *S. aureus* (MSSA) pneumonia treated with vancomycin have been associated with mortality rates of 50 and 47 %, respectively [8], whereas MSSA pneumonia treated with β-lactams has been associated with only 5 % mortality [9, 10]. Many reasons are accounted for these unsatisfactory results.

The vancomycin molecule is relatively large and penetrates poorly and slowly into the alveolar lining fluid (ALF) as well as into alveolar macrophages. As a result, levels attained in ALF are only one-sixth of the plasma concentration [11–13]. Higher vancomycin trough serum concentrations of 15–20 mg/mL than do conventional trough levels of 5–15 mg/mL has been proposed in order to have better therapeutic outcomes. However, experience suggests that patients with high vancomycin trough serum levels and high serum vancomycin areas under the curve (AUCs) have outcomes similar to those of patients with lower vancomycin serum levels [14, 15]. Low efficacy of vancomycin may also be associated with the drug's reduced bactericidal activity against MRSA strains with higher, although still susceptible, vancomycin MICs (1 or 2 mg/mL) [16].

Based on these findings, the recent vancomycin therapeutic monitoring guidelines recommend more aggressive vancomycin dosing schemes, maintaining vancomycin troughs between 15 and 20 mg/L "based on the potential to increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections caused by *S. aureus*" [17].

Pharmacodynamics data suggest that a near maximal bactericidal effect is achieved against MRSA when the ratio of the vancomycin area under the concentration-time curve and the minimum inhibitory concentrations (AUC/MIC) exceeds 400 [18]. However, total daily doses of vancomycin <4 g were not able to achieve an acceptable probability of target attainment (PTA) for infections with a MIC value of 2 mg/L. For infections with an MIC value of 1 mg/L, only aggressive doses of vancomycin were able to achieve a satisfactory PTA but with a high risk of nephrotoxicity, especially for patients residing in the ICU and or patient with renal hyperfiltration. Considering that the prevalence of patients with MRSA infections with MIC values 1 mg/L is increasing alternative anti-MRSA agents should be considered.

Linezolid has approved label indication for nosocomial MRSA pneumonia. Linezolid is an oxazolidinone that inhibits the formation of the 70S initiation complex by binding to the 23S ribosomal RNA of the 50S subunit, thus preventing translation.

Linezolid, unlike vancomycin, has favorable lung pharmacokinetics, with AUC/MIC in the ALF of $\sim$120, Cmax/MIC in the ALF of 16.1, and concentrations in the ALF that exceed the linezolid MIC for MRSA during the entire dose-to-dose interval [19].

Two large prospective, randomized, double-blind trials found that linezolid was statistically noninferior to fixed-dose vancomycin (1 g twice daily) for the treatment of staphylococcal VAP and HAP [20, 21]. Post-hoc analysis of both trials combined found that survival (80.0 vs. 63.5 %; *P* 5.03) and clinical cure (59.0 vs. 35.5 %; $P < 0.01$) were significantly improved in the MRSA pneumonia subgroup when treated with linezolid, compared with vancomycin [22], including patients with MRSA VAP.

These analyses have received much criticism particularly because the vancomycin groups received fixed doses of 1 g every 12 h rather than weight-adjusted doses to target therapeutic trough concentrations. In addition, a study of patients with MRSA infections found no significant difference in efficacy between vancomycin and linezolid in the intention-to-treat population (60.2 vs. 62.4 %, respectively) [23].

A recent large, randomized, double-blind, controlled trial was conducted to prospectively assess the efficacy, safety, and tolerability of fixed-dose linezolid, compared with dose-optimized vancomycin for the treatment of proven MRSA nosocomial pneumonia in hospitalized adults has been completed and published [24].

This trial demonstrated greater clinical efficacy (primary trial end point) of linezolid, compared with adjusted-dose vancomycin, for the treatment of MRSA nosocomial pneumonia. The results confirm the pattern of clinical efficacy seen in prior subgroup analyses of studies comparing linezolid with vancomycin in nosocomial pneumonia. clinical response was significantly better with linezolid than with vancomycin and MRSA clearance at the end of treatment was 30 % greater with linezolid than with vancomycin. However, no statistically significant differences in mortality were demonstrated. Tolerability profiles of both agents appeared to be equivalent, although, as expected, nephrotoxicity was more common with vancomycin.

12.2 Vancomycin or Linezolid?

Available data suggest that linezolid is not likely to be inferior to optimally dosed vancomycin and may be superior. Based on the currently available evidence and cost-effectiveness, vancomycin (with a loading dose of 15 mg/kg and trough level of 15–20 mg/mL) can be used in younger patients with normal renal function for pneumonia caused by MRSA strains with vancomycin MICs until 0.5 mg/mL. For patients with pneumonia caused by MRSA strains with vancomycin MICs 1.0 mg/mL, linezolid at 600 mg every 12 h is suggested as first line therapy. Moreover linezolid should be considered in patient who require concomitant nephrotoxic therapy or who have preexisting renal failure.

12.3 Conclusions

The frequency of pneumonia caused by HA-MRSA and CA-MRSA is increasing often with numerous complications, and high mortality rates. HA-MRSA pneumonia is a frequently fatal illness that occurs in older, debilitated patients, especially those who are receiving ventilator support. The rapid institution of effective therapy is essential to change the mortality rate for these diseases. Unfortunately, the rapid determination of the etiology of severe pneumonia is possible only in a limited number of cases, therefore broad-spectrum antibiotic therapy that will treat infection with MRSA as well as other potential pathogens should be instituted early. However, if the pathogen is detected, descalation therapy is warranted. While there are several antimicrobial agents available with MRSA activity, only linezolid has demonstrated noninferiority or possible superiority to vancomycin in the treatment of nosocomial MRSA pneumonia. From a cost perspective, even when considering the additional laboratory monitoring costs of drug concentrations, vancomycin is likely the preferred option in most institutions. However, there are clinical scenarios in which linezolid may be more appropriate. First, for patients with documented MRSA isolates with vancomycin MIC > 1 μg/mL, linezolid should be used in addition, therapy for patients who fail to clinically respond to vancomycin or those who develop vancomycin-induced nephrotoxicity should be switched to linezolid.

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The Role of Microbiology for Diagnosis of Fungal Infections

13

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The incidence of the *invasive fungal infections* (IFIs) has notably increased over the last few years, above all in critical and immunodepressed patients who account for 70−80 % of all the cases of opportunistic systemic mycosis following the increase in the number of risk factors that predispose for these infections [1].

The diagnosis of IFIs is often complicated following the absence of specific signs and symptoms, especially in the early phases of the disease. For these reasons the European Organization for Research in the Treatment of Cancer/Mycosis Study Group (*EORTC/MSG*) proposed and has updated the criteria for the definition of IFIs, considering various clinical, and diagnostic aspects [2]. According to EORTC, invasive fungal diseases (IFD) can be classified as certain, probable, or possible. As regards certain and probable IFDs laboratory investigations play an important role. In particular, the certain diagnosis of IFD still remains based on classic diagnostic methods that use microscope observation of fungal elements in host tissue or sterile material, isolation in culture from sterile sites, and the investigation of the antigen *Cryptococcus* in serum.

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13.1 Classic Diagnostic Methods

The diagnostic meaning of direct laboratory tests is closely correlated with the clinical sample and the fungus involved. In fact, considering the invasiveness of the procedure needed to obtain biopsies, very often these investigations are carried out on clinical samples in which microscopic observation and isolation of colonies of *Candida* or *Aspergillus* are not necessarily associated with invasive infections but often with colonization of the mucosa.

Classic diagnostic methods, such as direct microscopy, histopathology, and culture, have a limited sensitivity to detect IFIs, and their usefulness depends on the possibility of obtaining samples of deep tissues which, in many cases, cannot be taken due to the patient's condition. Therefore, these approaches must be considered as essential investigations to be performed when possible [3–6].

13.1.1 Microscopy

In direct preparations, fungal elements may be misinterpreted as artifacts when stained with Gram or hematoxylin–eosin. Hyphae are best visualized by 'special fungal' stains. Hence, bronchoscopic material or tissue biopsies should be examined with periodic acid–Schiff, Grocott's methenamine silver, or optical brighteners (e.g., calcofluor white). Body fluids from normally sterile sites must be obtained and collected aseptically and transported to the laboratory promptly. The use of optical brighteners is recommended for microscopical examination of unfixed specimens. *Microscopic examination* of body fluids from normally sterile sites, such as blood, can be a rapid and specific method for the diagnosis of proven IFIs. However, microscopic examination has a low sensitivity, requires expertise for interpretation, and morphology cannot be used for definitive identification.

13.1.2 Culturing Techniques and Fungal Identification

Blood cultures (BCs) are essential for diagnosing candidaemia despite their low sensitivity. The problems connected with low sensitivity are attributable to several factors: (i) the number of BCs and the timing to obtain them and the total volume to be taken, (ii) permanence of *Candida* in the blood, and (iii) the BC system used. A panel of experts of the European Fungal Infection Study Group (EFISG) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) undertook a data review and compiled guidelines for the recommendations for taking and processing of blood samples to ensure the optimal isolation of microorganisms [7]. In particular, the number of BCs recommended in a single session is 3 (2–4), with a total volume varying according to the age of the patient, 40–60 mL for adults, 2–4 mL for children under 2 kg, 6 mL between 2 and 12 kg, and 20 mL between 12 and 36 kg. The timing to obtain the BC is one right after

the other from different sites, and venipuncture remains the technique of choice. BC set comprises 60 mL blood for adults obtained in a single session within a 30 min period and divided into 10 mL aliquots in three aerobic and three anaerobic bottles. BC sensitivity varies depending on the species and system used. *Lysis-centrifugation* procedures show a higher efficacy when other emerging and rare yeast pathogens are found in the blood of patients with fungemia [8]. Despite these recommendations, the accuracy of BCs is not very high since candidaemia can be transient and go undetected.

All fungi recovered from sterile sites should be identified down to the species level. Most yeasts isolated from clinical samples can be identified using one of the numerous commercial identification systems, such as API 20C AUX, VITEK 2, and RapID Yeast Plus, this takes an additional 48−72 h to complete after the yeast-like fungal pathogens are observed in the blood culture media [9, 10]. Unlike pathogenic yeasts, filamentous fungi can be identified only by visualization of macroscopic or microscopic morphologic characteristics, following sub-cultivation of a mold isolate to encourage sporulation, a process that takes from days to weeks [9]. Various molecular techniques, including fluorescent in situ hybridization and pyrosequencing, have been developed to speed up the *identification* of blood-borne fungi, but they have not been implemented as routine techniques in the clinical microbiology laboratory [11, 12]. Matrix-assisted laser desorption ionization–time of flight mass spectrometry has been described as a useful tool for rapid routine identification of clinical yeast and *Aspergillus* isolates [13, 14]. Recently, the Matrix-Assisted Laser Desorption Ionization Biotyper System has been successfully applied for identification of yeast species directly from positive BCs, with important implications for appropriate management of patients suffering from fungemia [15].

13.2 Nonculture Methods

To facilitate early diagnosis of IFIs and to make an early therapeutic intervention in an attempt to reduce the high mortality associated with invasive fungal infections, alternative procedures based on the detection and quantification of fungal biomarkers have been developed. In particular, galactomannan [GM] and 1,3-beta-d-glucan [BG] were included in the EORTC/MSG diagnostic criteria for invasive fungal infections for all types of patients. In the EFISG guidelines the combined use of mannan and anti-mannan antibodies in serum is also recommended for the diagnosis of candidaemia, while the detection of other antibodies, the septifast test, and in-house PCR are not recommended because no data are available evaluating their usefulness for the clinical diagnosis of candidaemia.

13.2.1 *Aspergillus* Galactomannan Antigen

GM is a component of the fungal cell wall that can be detected by a sandwich type enzyme-linked immunosorbent assay (ELISA) in serum samples, bronchoalveolar lavage (BAL) fluid samples, and cerebrospinal fluid. The current cut-off for optical density index for positivity is 0.5, though results of the The Platelia™ *Aspergillus* Ag in BAL fluid samples between 0.5 and 1.0 index have a lower predictive value than BAL sample results >1.0 index values, hence the results between 0.5 and 1 index values should be reviewed and supported by other clinical, radiological, or laboratory evidence of invasive aspergillosis. The Platelia™ *Aspergillus* Ag is a test which, when used in conjunction with other diagnostic procedures such as microbiological culture, histological examination of biopsy samples and radiographic evidence can be used as an aid in the diagnosis of invasive aspergillosis. The sensitivity and specificity of the test is conditioned by several factors, including the impact of prior antifungal therapy, the occurrence of false-positive results in association with β-lactam antibiotics (e.g., piperacillin–tazobactam), and in patients receiving products containing *galactomannan*, either parenterally or orally in the presence of an alteration of the intestinal barrier.

13.2.2 1,3-beta-d-glucan Antigen

1,3-beta-d-glucan antigen (BG) is a cell wall constituent of several fungi, including *Candida*, *Aspergillus*, *Fusarium*, *Acremonium,* and *Pneumocystis jiroveci*. However, BG concentrations are usually low or absent in patients with cryptococcal infections, and BG is usually absent in patients with zygomycosis since these fungi do not produce BG. Currently, 3 photometric BG assays kits are commercially available for diagnostic use: *Fungitell* (Associates of Cape Cod, East Falmouth, MA, USA), Fungitec-G (Seikagaku Biobusiness, Tokyo, Japan), β-Glucan Test (Maruha, Tokyo, Japan). In Europe and America, the most used is Fungitell with a cut-off value of 80 pg/mL. A meta-analysis showed that the BG assay had a sensitivity and a specificity of 76.8 and 85.3 %, respectively [16]. The performance of BG testing for the detection of systemic *Candida* infection did not differ considerably from its performance for the detection of invasive aspergillosis [16]. The diagnostic performance of BG testing for IFIs seems to be similar to that of galactomannan detection used for the diagnosis of invasive aspergillosis, though few studies have performed direct comparisons of the 2 tests for the diagnosis of invasive aspergillosis in the same patients. The use of albumin, antibiotics such as amoxicillin-clavulanate or piperacillin-tazobactam, hemodialysis with cellulose membranes, presence of serious bacterial infections, use of surgical gauzes containing glucan, or severe mucositis are associated with false positives. Therefore, certain issues regarding the clinical usefulness of BG testing have not been well clarified, including the timing and the frequency of BG testing for at-risk patients, as well as the criteria. The currently used cut-off of 80 pg/ml appears to be acceptable however; it has been shown that values above 160 pg/ml are highly

indicative of candidemia [17]. Moreover, in a study of a systematic survey of BG levels in surgical ICU patients when the number of positive samples required to make a diagnosis was increased to two or three, the specificity increased without experiencing a decrease in sensitivity [18]. The BG assay seems to be reliable as an aid in IFI diagnosis. However, its positivity or negativity should be interpreted very carefully and compared with clinical data. The timing of the assay is critical to allow for an early start of antifungal therapy.

13.2.3 Mannan Antigen and Anti-Mannan Antibodies

Among *Candida* antigens, mannan is a highly immunogenic polysaccharide bound to the yeast cell wall. It appears to be one of the main biomarkers for the diagnosis of invasive candidiasis. Platelia™ *Candida* Ag Plus is a one-stage immunoenzymatic sandwich microplate assay, detecting the circulating mannan *Candida* antigen in human serum or plasma. Even in cases of invasive candidiasis, the mannan antigen is more difficult to detect in patients tested positive for the anti-mannan antibody. In a study that evaluated the use of the Platelia *Candida* antigen kit for the diagnosis of invasive candidosis in preterm infants a greater sensitivity of the test was highlighted, probably due to the absence of circulating anti-mannan antibodies in these patients [19]. It is important to note the low sensitivity for the detection of *C. parapsilosis* and *Candida krusei* infection. This difference in the sensitivity for antigenic detection of different species is consistent with the nature of the *Candida* mannose epitope recognized by the EBCA1 monoclonal antibody used in the test. The combined detection of *mannan and anti-mannan antibodies* is considered to be a method for specific detection of *Candida* spp. in serum samples [20].

13.2.4 *Candida albicans* IFA IgG for Germ Tube Antibody Detection

This test is based on the detection, by an indirect immunofluorescence assay, of antibodies against the surface of *C. albicans* germ tubes *Candida albicans* IFA IgG for germ tube antibody detection (CAGTA). The test provides a rapid and simple diagnosis of invasive candidiasis (IC) in the clinical microbiology laboratory [21]. The performance of the test has been studied in hematological patients (87.5 % sensitivity and 95.2 % specificity) [22], and recently in ICU patients [23–25]. In particular, in these publications a significant decrease in mortality in ICU patients with a CAGTA-positive result was shown especially in those with increasing CAGTA values who had been treated with antifungals [23, 24]. Also, previous surgery was identified as the principal clinical factor associated with CAGTA-positive results [25]. The CAGTA detection assay has been used in combination with (1→3)-β-D-Glucan, C-reactive protein, and procalcitonin for discriminating between *Candida* spp. colonization and IC in non-neutropenic critically ill patients with severe abdominal conditions and to establish a model for the prediction of IC

[26]. This study shows that BG levels greater than 259 pg/mL combined with CAGTA-positive results accurately discriminate *Candida* spp. colonization from IC in non-neutropenic critically ill patients with severe abdominal conditions [26]. Therefore, although this test is not recommended because few data are available, the detection of CAGTA may be important for the diagnosis of invasive candidiasis in hematological and surgical patients admitted in ICUs.

13.2.5 Molecular-Based Detection Methods

A range of polymerase chain reaction (PCR)-based methods have been developed with the prospect of giving highly specific, highly sensitive, and rapid means for fungal detection and identification [27]. There are some commercial molecular methods for fungal DNA detection. LightCycler® *SeptiFast Test* (Roche Molecular Diagnostics, USA), provides rapid detection and identification of bloodstream infections by real-time PCR directly from blood. In particular, SeptiFast detects up to 25 microorganisms including five *Candida* species (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*) and *Aspergillus fumigatus*. Another commercial molecular method for fungal DNA detection is *MycAssay kits* (Myconostica Ltd, UK), and in particular one detects *Aspergillus* DNA (15 species) in serum or BAL, and another detects *P. jiroveci* DNA in respiratory samples. Also in-house PCR combined with classical diagnostic methods can improve early diagnosis of IFIs. In particular, in a study performed on preterm neonates in neonatal ICUs with suspected candidaemia the detection of fungal DNA directly from blood culture Isolator 1.5 microbial tubes, without prior cultivation, has been a promising approach for the rapid detection of *Candida* sp. [28].

However, several questions need to be addressed before the molecular methods can be adopted in daily clinical routine; these include (i) which DNA targets are best for commercial kits used in routine diagnostic laboratories, (ii) what the optimal methods are for extracting *fungal DNA* from clinical specimens obtained from various sites, and (iii) which detection methods are best for routine use. Molecular diagnostic methods may not distinguish individuals who are colonized from those who are infected. However, molecular detection methods, combined with additional microbiological and clinical information, have the potential not only to accurately and rapidly identify fungal pathogens, but also to indicate whether the pathogen is likely to respond to conventional antifungal treatment.

13.3 Conclusions

The role of microbiology in the diagnosis of IFIs is becoming ever more strategic in relation to the typology and clinical conditions of the patient as well as the clinical samples that can be obtained for laboratory tests. In the clinical samples where the presence of fungi indicates infection, microscopy and isolation in culture are both necessary even with the above mentioned limits. The microscopic

examination is rapid and low cost, isolation in culture identifies important epidemiological and therapeutic implications following identification of the etiological agent, and detection of virulence factors and the state of in vitro sensitivity. Thanks to the introduction of non-culture methods using biomarkers in association with the patient's clinical data, today it is possible to make an early diagnosis of IFIs that overcomes the limits connected with the low sensitivity of the culture method and the difficulty of obtaining bioptic samples not routinely available from patients who have serious risk factors. The use of an *integrated diagnosis* that associates conventional methods with the use of biomarkers seems to be important for a rapid and accurate diagnosis of IFIs. In fact, thanks to the advances in the study of pathogenesis, to the introduction of rapid and sensitive diagnostic tests, today it is possible to establish appropriate criteria for the selection of patients to undergo a specific diagnostic workup that allows a rapid, early diagnosis of invasive fungal diseases and favors diagnostic-driven strategy.

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Sepsis and Organ(s) Dysfunction

Ongoing Challenges Translation Research

14

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14.1 Background

Sepsis is one of the most significant causes of morbidity and mortality in intensive care units (ICUs) [1]. The incidence of sepsis is still frequent, and the high mortality rates associated with the disease is increasing in the critically ill. Worldwide, 13 million people become septic each year and 4 million die [2, 3].

The pathophysiology of sepsis remains an enigma [4] and the natural history is ever evolving. The management of sepsis is complex and represents a real challenge for patient survival.

Sepsis involves a complex interaction of innumerable factors, some of which may be difficult to identify, and definitive targeted treatment is a very difficult goal. The diagnosis of sepsis is still a major challenge because its clinical signs (tachycardia, tachypnoea, leukocytosis or leukopenia, hypothermia, or hyperthermia) are very aspecific and blood cultures in septic patients may be positive only in approximately 30–40 %. This review discusses the search for effective therapeutic interventions, hurdles in translational sepsis research, and new therapies in development of the clinical trials.

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14.2 Spectrum of Sepsis Definition

See Table 14.1.

14.3 Key Points in Sepsis

14.3.1 Signs and Symptoms

Diagnosis of sepsis represents a true challenge for the prevalence of aspecific signs. Clinical evolution is often misleading; furthermore, the presence of biological markers remains an elusive concept.

14.3.2 Endothelium, Cytokines, and Immunosystem

Microcirculation dysfunction, during a picture of severe infection, is not the consequence of a single molecule activity but a complex cascade, such as an endothelial explosion of mediators with pro-inflammatory and anti-inflammatory response. In other words, the endothelium promotes a condition of systemic inflammation determining a profound change in the cellular and organ function.

Table 14.1 Surviving Sepsis Campaign (SSC): Sepsis' and MODS' definition

Infection Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
Systemic inflammatory response syndrome (*SIRS*) The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: (1) temperature >38 °C or <36 °C; (2) heart rate >90 beats per minute; (3) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a $PaCO_2$ of less than 32 mm Hg; and (4) white blood cell count >12,000/mm^3, <4,000/mm^3, or >10 % immature (band) forms [5, 6]
Sepsis The a systemic inflammatory response to an active infectious process in the host., manifested by two or more of the following conditions as a result of infection: (1) temperature >38 °C or <36 °C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg; and white blood cell count >12,000/mm^3, <4,000/mm^3, or >10 % immature (band) forms
Severe sepsis Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, acute alteration in mental status
Septic shock Sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured
Multiple organ dysfunction syndrome (*MODS*) Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

The endothelium releases several mediators (interleukins, TNFα); while the macrophage migration inhibiting factor and chemokines are able to stimulate the expression of different adhesion molecules, with an impact on the circulation, kidney, lung, liver, central nervous system, and the coagulation cascade. Therefore, the tissue damage/insult is mediated by the macrophages, cytokines, and the endothelial cells.

Cytokine levels may seem an obvious choice as cytokines are key mediators of the inflammatory response to sepsis. Raised levels of certain cytokines have been well documented in patients with sepsis and some have been correlated with outcome. The most important pro-inflammatory mediators are the tumor necrosis factor, (TNF), Interleukin 1 (IL-1), Interleukin 4 (IL-4), Interleukin 6 (IL-6), and Interleukin 8 (IL-8) [7].

The cytokines have pleiotropic functions mediated by the immuno system, which is linked to the several biohumoral response of the host. The understanding of these physiological networks will depend on the exact clinical circumstances, which in turn will elicit a biological response from the targeted cells and cytokines which express either as a positive or a negative signal [8].

14.3.3 Coagulation

Activation of the coagulation system assumes a key role in sepsis. Markers that define the pro-inflammatory state are represented by the coagulation parameters; since the pro-inflammatory state is accompanied by a pro-coagulative and anti-fibrinolytic state.

One of the critical aspects in sepsis is the alteration of the coagulation system. The coagulation system activation does not follow the classical cascade mechanism but rather a cellular mechanism, where the tissue factor (TF) complexing with factor VIIa on the membrane surface is the main stimulus of coagulation in vivo, followed by a massive increase in thrombin formation by the prothrombin complex expressed by factors Xa and Va.

The activation of the coagulation pathway by the tissue factor (TF) leads to the enhancement of the coagulation process and the simultaneous impairment of coagulation inhibiting mechanisms. Suppression of the fibrinolytic system results in a pro-coagulant state, which may lead to the formation of thrombi in the microcirculation reducing organ perfusion and causing organ dysfunction. The activation of coagulation cascade play an active role, not entirely understood.

The monitoring of the natural coagulation inhibitors: antithrombin III (ATIII) and C anticoagulant protein, as well as a count of the platelets and the D-dimer are mandatory if associated with other markers like the TAT complex (thrombin/antithrombin), the 1 + 2 fragment, and the PAP complex (plasmin/antiplasmin) to understand the dynamic process of coagulation derangement during sepsis.

The screening tests and confirmatory tests are routinely recommended to monitor coagulation system confirming a prevalence of fibrinolysis or a condition

Table 14.2 Screening and confirmatoy tests in the diagnosis of consumption cagulopathy (DIC)

Screening tests	Prothrombin time
	APTT
	Platelets
	Fibrinogen INR
Confirmatory tests	Soluble fibrin monomer complex
	Fibrinogen degradation products
	D-dimer
	Prothrombin fragments 1 and 2
	Antithrombin III

of microvascular thrombotic process with secondary hemorrhage occurring or when platelets and clotting factors are sufficiently depleted (Table 14.2).

14.3.4 DO_2-Oxygen Delivery

Peripheral arterial vasodilatation and the increase in the cardiac capacity (hyperdynamic state) are considered as the main cause of alterations in the tissue capturing oxygenation. Moreover, the disorders in the microcirculation and peripheral shunting of oxygen are responsible of the tissue oxygen extraction (dysoxia), which increases the blood level of lactic acid.

Early hemodynamic assessment on the basis of preload, afterload, and contractility is useful to detect balance between systemic oxygen delivery and oxygen demand; end points used to confirm the achievement of such a balance include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH. Early goal-directed therapy provided at the earliest stages has significant benefits from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand.

Early lactate clearance as a surrogate for the resolution of global tissue hypoxia is significantly associated with decreased levels of biomarkers, improvement in organ dysfunction, and a better outcome in patients suffering sepsis [9]. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. These findings support a growing body of evidence suggesting that global tissue hypoxia plays a crucial role in the complex mechanisms causing abnormal activation of endothelial response in sepsis.

14.3.5 Hyperlactacidemia

In the critically ill, a high blood level of lactate concentration is associated with a higher risk of death [10]. The amount of lactate produced is believed to be in relationship with the total oxygen debt, the magnitude of hypoperfusion, and the severity of shock.

Patients developing a condition of severe sepsis or septic shock commonly demonstrate a condition of hyperlactacidemia associated with haemodynamic perturbations leading to global tissue hypoxia. Early lactate clearance as a surrogate for the resolution of global tissue hypoxia is significantly associated with decreased levels of biomarkers; a better tissue perfusion decrease organ dysfunction and allow a better patients outcome [11].

14.4 Grading Severity of Sepsis, Immunosystem, and Scoring Index

The inflammatory response is a highly orchestrated system of the cellular activity and locale release of pro-inflammatory and anti-inflammatory response. Pro-inflammatory and anti-inflammatory mediators act as opposite forces, with frequent imbalance between them (Fig. 14.1).

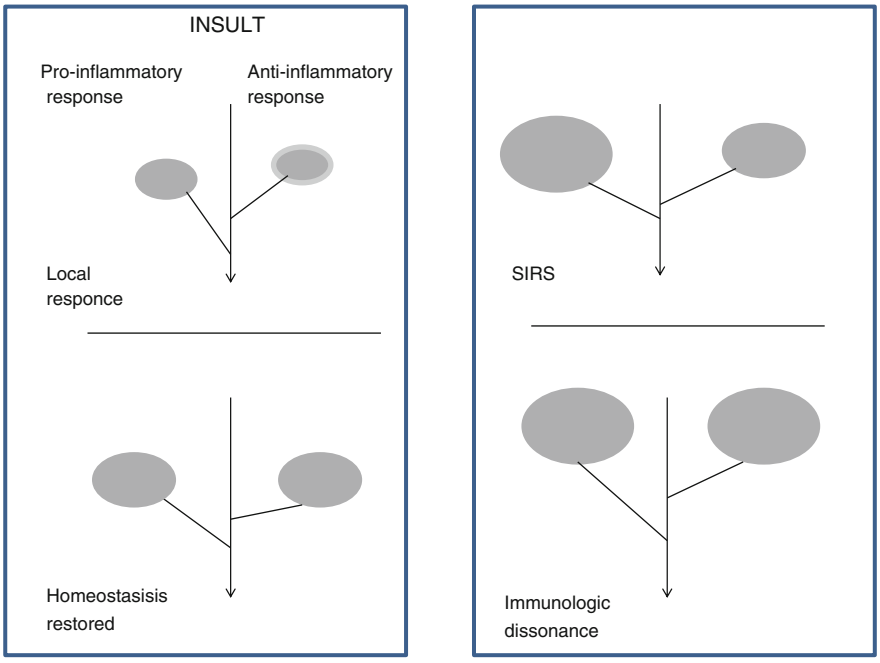

Fig. 14.1 Pro-inflammatory and anti-inflammatory response. Modified from [12]

A balancing of these mediators in the micro-environment results in regained homeostasis, failing which a massive pro-inflammatory reaction (SIRS) may set in and, together with other biohumoral factors, lead to severe organ or system impairment.

The immune response is a regulated cellular activation system involving the release of pro- and anti-inflammatory mediators. The complex pathophysiology of sepsis encompasses the interplay of pro- and anti-inflammatory cells, disrupted coagulation, endothelial activation and injury, vasodilatation and vascular hypo-responsiveness to vasoactive mediators, cardiac dysfunction, and cellular dysoxia.

The pathophysiological mechanisms involved are complex and the various biohumoral interactions or mediators action mechanisms are not fully understanding. The immune system is a key factor in sepsis progression. The complexity of the host defence system and the development of a multiple modality approach at various steps includes components of immune modulation and immune enhancement and abnormalities or imbalances in the host homeostasis pro-inflammatory versus anti-inflammatory status.

The understanding of the interplay between the host's immune, inflammatory and pro-coagulant responses in sepsis is essential to the development of diagnostic and management strategies.

The mediators of inflammatory cascade not only reduces systemic vascular resistance but also causes myocardial depression and left ventricular dilatation with decreased ejection fraction. As the inflammatory response progresses, myocardial depression becomes more pronounced and may result in a falling cardiac output.

The endothelial cell and microcirculatory dysfunction and the subsequent tissue hypoperfusion contributes to multiorgan failure and cellular dysfunction. In addition, there is fibrin deposition and microvascular thrombosis, caused by alterations in the coagulation cascade towards a prothrombotic and antifibrinolytic state, which may threaten end organs.

A severe complication of SIRS is the development of organ system dysfunction, as acute lung injury, renal failure, and multiple organ dysfunction syndrome (MODS). MODS or sequential organ dysfunction/multiple organ dysfunction, and multiple systems organ dysfunction describe an evolving clinical syndrome characterized by the development of otherwise unexplained abnormalities of organ function.

Once multiple organ dysfunction occurs, chances for survival decrease. Thus whether the mortality can be greatly reduced will depend more on preventing multiple organ dysfunction from developing rather than treating it after occurs. Organ dysfunction is influenced by several factors such as age of the patient, functional impairment, severity of the aggression, and consequent alterations of microcirculation and by the direct or mediated effect of the insult in a state of immune system impairment.

The evaluation of severity of organ dysfunction is made through the use of scores and prognostic models. The aim is stratifying patient based on the severity of illness and scoring systems are the instruments. Prognostic models predict the

outcome based on a given set of prognostic variables and a modeling equation. Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity of the basic phenomenon of inflammation. Sepsis is a multifactorial and dynamic syndrome that can develop into conditions of different severity, described as severe sepsis or septic shock. Sepsis, severe sepsis and septic shock, associated with grading of organ dysfunction has been reported to be a conditions that limit quality of life and the most common cause of death in ICU. The use of specific severity indexes has proved helpful also to establish the prognosis (Table 14.3).

The development of scoring system started in 1980, and the first score was the Acute Physiology and Chronic Health Evaluation. Two years later was published a simplified version of this model the simplified acute physiology score (SAPS). Another simplification of the original APACHE system the APACHE II was published in 1985 [13].

This system introduced the possibility to predict mortality. Scoring system as a means of mortality risk-severity of illness prediction has evolved. Further prospective studies will be necessary for evaluating the best scores or combinations of scores. The PIRO model remains a hypothesis-generating model for future research.

SOFA score SOFA (Sequential Organ Failure Assessment) score is one of the scores available for assessing the severity of organ dysfunction [14] in contrast to older scores the SOFA score doesn't predict outcome but describe organ dysfunction. It represents an important sequential index to evaluate the entity of organ dysfunction or the improvement of clinical conditions. Although the final score expresses the level of morbidity rather than the mortality index.

SOFA consider six organs with a scale from 0 to 4 (worse situations) using parameters readily available and routinely measured in most ICUs (Table 14.4). This score is useful as an early prognostic indicator. SOFA Score is obtained through the arithmetical sum of the score assigned to each organ system.

Prognostic relevance of the SOFA score in combination with inflammatory parameters was also found in a recent study conducted by Zügel et al., even though results were based on only a small number of events [15].

Table 14.3 Measurable parameters of organ system function

Organ system	Measurable parameters
Central nervous	Glasgow coma score
Respiratory	PaO_2/FiO_2
Cardiovascular	Blood pressure
Hematologic Renal	Platelet count
Hepatic	Serum bilirubin
Kidney	Serum creatinine
Gastrointestinal	No appropriate one

Table 14.4 The Sequential Organ Failure Assessment (SOFA) score

SOFA Score	1	2	3	4
Respiration PaO_2/FiO_2	<400	<300	<200	<100
Coagulation Platelet count (×1000/μL)	<150	<100	With respiratory support <50	With respiratory support <20
Liver Bilirubin (mg/dL)	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular hypotension	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine ≥5 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system GCS	13–14	10–12	6–9	<6
Renal creatinine (mg/dL) or Urine output	1.2–1.9	2.0–3.4	3.5–4.9 or <500 mL/day	>5 or <200 mL/day

Six organ system are evaluated on a Scale of 1–4 each, according to he criteria indicated. SOFA score is obtained through the arithmetical sum of the score assigned to each organ system [14]
[a]Adrenergic agents administered at least 1 h (doses given are μg/Kg/min)
MAP mean arterial pressure, *GCS* Glasgow coma scale

APACHE II ("Acute Physiology and Chronic Health Evaluation II") is a severity-of-disease classification system [13] is commonly used to establish illness severity in the ICU and predict the risk of death. It is applied within 24 h of admission of a patient to an ICU. There is an inverse relationship between the high score and the length of stay; higher scores correspond to more severe disease and a higher risk of death. The model uses the most deranged value from the first 24 h in the ICU of 12 physiological variables (scored from 0 to 4 points), age, surgical status (emergency, scheduled), and previous health status (Table 14.5).

14.4.1 APACHE Score

The APACHE II score combines variables according to which a numeric score is allotted (from 0 to 71 based on several measurements). Patients with low APACHE II scores (i.e., 0–8 and 9–12) had mild and moderate signs and symptoms of sepsis (one or two out of four). Median APACHE II score was 13–16, patients with this score had moderate severe signs and symptoms of sepsis (i.e., 2–3 out of 4).Patients with higher scores (17–20 and 21–25) had mostly severe signs and symptoms.

Table 14.5 Acute Physiology and Chronic Health Evaluation II (APACHE II)

Physiologic variable	High abnormal range					Low abnormal range				Points
	+4	+3	+2	+1	0	+1	+2	+3	+4	
Temperature (°C)	>41°	39°–40.8°		35.5°–38.4°	36°–38.4°	34°–35.8°	32°–33.9°	30°–31.9°	<29.9°	
Mean arterial pressure (mm Hg)	>160	130–159			70–109		50–69		<49	
Heart rate (ventricular response)	>180	140–178			70–109		55–69		<3	
Respiratory rate (non-ventilated or ventilated)	>50	35–49			12–24		6–9		<5	
Oxygenation: A-aDO_2or PaO_2 (mm Hg) a. $FIO_2 \geq 0.5$ record A-aDO2 b. $FIO_2 < 0.5$ record PaO2	>500	350–498	200–349		<200	200–349				
					PaO2 > 70	PaO2 61–70		PaO2 55–60	PaO2 < 55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	>7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.15–7.32	7.15–7.24	<7.15	
	>52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15	
Serum sodium (mEq/l)	>180	160–179	155–159	150–154	130–149		120–129	111–119	<110	
Serum potassium (mEq/l)	>7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5	
Serum creatinine (mg/dl) Double point score for acute renal failure	>3.5	2–3.4	1.5–1.9	0.6–1.4			<0.6			
Hematocrit (%)	>60		50–59.9	48–49.9	30–45.9		20–29.9		<20	
White Blood Count (total/mm3) (in 1000 s)	>40		20–39.9	15–19.9	3–14.9		1–2.9		<1	
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS									
Total Acute Physiology Score (APS) Sum of the 12 individual variable points										

14.4.2 PIRO Score

The acronym PIRO refers to some important aspects related to sepsis: predisposition, infection, host response, and organ dysfunction. The PIRO is a staging system that was proposed for the purpose of incorporating both host factors and response to a particular infectious insult (Table 14.6).

Predisposition assumes a key role of individual genetic characterization, and evidence the importance of factors able to increase the risk of infection and mortality as a consequence of sepsis. Infection is the second key point and includes several elements such as bacteria type, infection localization, and the seriousness of the infection. Response is the third element and means the host's capacity to react to the septic. Organ dysfunction is the last but not the least factor considered in the PIRO model. PIRO is a model designed to stage as well as monitor the host response to infection on the basis of factors believed to be pertinent to outcomes. The concept, termed Predisposition, Infection, Response, Organ dysfunction (PIRO) was elaborated to define, diagnose, and treat patients with sepsis [16].

The PIRO scoring system has been introduced starting with the concept of similarities existing between cancer and sepsis: complex pathophysiological mechanisms, organ or systemic involvement, different medical and surgical treatment strategies, high indices of mortality, and high cost of treatment. Whether the PIRO system will evolve into a useful tool for bedside clinicians will depend on the results of future investigations and epidemiologic studies. Multiplex technology or combinations of elements in scoring systems are two approaches that can improve the diagnosis of sepsis, but further research is needed in this field [17].

14.5 Early Goal Directed Therapy

Rivers et al. [18] showed that the early goal directed therapy (EGDT) aimed at normalizing hemodynamic parameters and reversing global tissue hypoxia in the pre-ICU period for severe sepsis and septic shock patients significantly decreases morbidity and mortality. These studies support that improving morbidity and mortality heavily depends on early recognition and treatment of high risk patients [19].

Table 14.6 PIRO scores and clinical factors

PIRO scores	Clinical factors
Predisposition	Age, concomitant disease, use of steroids, or immune-suppressive treatment
Infection	Site of infection: pneumonia, peritonitis
Response	Body temperature and heart rate, arterial pressure and cardiac index
Organ (dysfunction)	GCS, arterial pressure, diuresis

Early recognition of sepsis and identifying at-risk patients are crucial in sepsis. International guidelines have been issued stating a series of recommendations for the early diagnosis and management of sepsis [20]. The infections (e.g., sepsis, bacteremia, and pneumonia) are time-sensitive and that survival is improved considerably when early and aggressive treatment, including early goal-directed therapy and early antibiotic administration, is provided. Failure to recognize the patient with sepsis and treat at this stage, prior to or early in the development of organ dysfunction, results in increased morbidity and mortality [21].

The importance of the EGDT aimed at normalizing hemodynamic parameters and reversing global tissue hypoxia in the pre-ICU period for severe sepsis and septic shock patients significantly decreases and improves morbidity mortality depending on early recognition and treatment of high risk patients. EGDT involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. Early (6 h) aggressive therapy to restore and maintain oxygen availability to the cells in sepsis, and the use of fluids and inotropic agents titrated by appropriate hemodynamic monitoring, is recommended. The trial of EGDT resulted in significant reductions in health care resource consumption, morbidity, mortality, and vasopressor use.

14.6 Source Control

Source control is the best way to reduce quickly the bacterial inoculum. Source control is an important aspect of the early management of septic patients. Appropriate source control should be part of the systematic checklist we have to keep in mind in setting up the therapeutic strategy of sepsis. Most recommendations are however, graded as C or D due to the difficulty to perform appropriate randomized clinical trials in this respect [22].

All patients presenting with severe sepsis be evaluated for the presence of a focus of infection amenable to source control measures, specifically the drainage of an abscess or local focus of infection, the debridement of infected necrotic tissue, the removal of potentially infected device, or the definitive control of a source of ongoing microbial contamination.

Key principles of source control:

- drainage of infected fluid collection,
- debridement of infected solid tissue and the removal of devices or foreign bodies, and
- definitive measures to correct anatomic derangements resulting in ongoing microbial contamination and to restore optimal function.

Source control technique (drainage, debridement, device removal, and definitive control) are essential in the therapeutic strategies of sepsis.

A patient with sepsis of unknown origin is a challenge for the physician. In this clinical setting, collaboration between surgeon and the intensivist, and radiological imaging is necessary to a successfully outcome [23]. In some circumstances, it

Table 14.7 Cure of sepsis focus

Cure of septic focus	Surgery
	Removal of infected catheter
	Fiberoptic bronchoscopy
	Antimicrobial drugs
	Relaparatomy

may be difficult or even impossible to identify the source of the infection which might otherwise be removed relatively simply, using proper antimicrobial treatment or a less invasive surgical removal of the area from which the infection originates based on needle-guided radiology (Table 14.7).

New tools need to be developed that specifically incorporate parameters indicative for ongoing abdominal infection, rather than merely ongoing organ failure, in patients with abdominal sepsis. Preferentially, these specific tools combine clinical findings, laboratory measurements and results from diagnostic imaging tests to assist the multidisciplinary team in selecting patients for re-intervention to treat ongoing abdominal infection.

14.7 Failure of the Clinical Trials

Over the last 15 years, there was a great interest in the potential of innovative therapy for sepsis, but unfortunately clinical trials have failed to demonstrate clinical efficacy due to study problems, dosing and timing therapy, and hetereogeneous patients population. Although many clinical trials have been performed, the available data are still controversial. The difficulty involved in comparing experimental data with clinical evidence has made the debate on sepsis and its sequelae highly controversial.

The monoclonal anti-TNF anti-body *(MAK).* The monoclonal antibodies (OKT3, OKT8, B1) allow for a detailed quantification in vitro of the lymphocyte subpopulations. MAK was targeted toward septic patients with increased interleukin-6 and report the following data: with 2,634 patients enrolled revealed a 3.6 % reduction in 28-day all-cause mortality with a p value of 0.49; but there are potential confounding variables. Today more and more attempts are being made to define the groups or subgroups of patients that could take advantage of adjuvant and immunomodulatory therapies.

As many clinical signs of sepsis are nonspecific and may even be misleading, a number of biomarkers have been proposed, such as circulating non-segmented neutrophils, acute phase proteins (C-reactive protein and neopterin), procalcitonin (PCT), cytokines (TNF-α, IL-6, chemochines, IL-8). These proved rather useful as diagnostic tools, but have a very poor specificity. Procalcitonin, IL-6 and other mediators may be used to guide clinicians to early diagnosis and assist in determining appropriate treatment strategies.

The significance of high serum procalcitonin concentrations as a sign of sepsis was first reported in 1993 and the authors proved helpful to identify patients with severe sepsis and septic shock [24]. High levels of procalcitonin have been reported in the literature in patients affected by severe bacterial infections, fungi, and parasites, when the endotoxin is in the circulation in sepsis and MODS. From a normal plasmatic concentration of <0.5 ng/ml, this level may rise several hundred times higher during severe sepsis and septic shock [25].

In addition, procalcitonin is a useful marker to distinguish between patients with SIRS and with sepsis. Procalcitonin cellular source, its regulation mechanisms and its mechanisms of interaction with bacteria and bacterial products are still unknown. However, serum concentration of this pro-hormone seems to have a higher prognostic value and it is helpful on guidance stop of antibiotic therapy [26, 27].

The future management of sepsis will most likely involve therapies directed at newer inflammatory targets. Several molecules are currently under investigation and include, among others: TLR4 [28–30], a cytokine-like molecule that promotes TNF release from mononuclear cells. Another important area of ongoing and future research lies in endothelial cells and the microcirculation. However, further clinical trials are needed to understand the various mechanisms activated in sepsis and the biohumoral interactions.

14.8 Surviving Sepsis Campaign and the Bundles

Supportive measure of care are needed to improve treatment standards in patients with sepsis. A group of experts of international scientific organisations promoted a general awareness-building campaign including guidelines for the treatment of sepsis [31].

The available information has been reviewed and analysed with a view to establishing a classification of severity using five levels of evidence, from A to E, (with level A representing the most robust evidence) and the various recommendations on prevention and treatment have been reported.

The publication of several randomized control trials demonstrating mortality reduction with certain interventions in severe sepsis, along with the desire to integrate evidence-based medicine into clinical practice, led to the development of the Surviving Sepsis Campaign (SSC) guidelines [31–34].

The task force of Survival Sepsis Campaign (SSC) reported several interventions or evidence-based manoeuvers showing a survival benefit in ICU patients [31–34].

The third edition of "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012" published in the February 2013 issues of Critical Care Medicine and Intensive Care Medicine, several tables summarizing again the recommendations and bundles which can be a useful tool in clinical settings.

The term bundles being a group of intervention related to a disease process that, when executed together result in better outcome than when implemented individually. Two bundles have currently been proposed:
6-h resuscitation bundle and
24-h management bundle.

14.8.1 Sepsis Resuscitation Bundles (6-h Bundles)

1. Serum lactate measured
2. Blood culture obtained before antibiotic administration
3. From the time of presentation, broad spectrum antibiotics administered within 3 h for ED admission and 1 h for non-ED ICU admission
4. In the event of hypotension and/or lactate >4 mmol/L (36 mg/dL)
   - deliver an initial minimum of 20 mL/Kg of crystalloids or colloid equivalent
   - Apply vasopressor for hypotension non responding to initial fluid resuscitation to maintain MAP >65 mmHg
5. In the event of persistent hypotension despite fluid resuscitation
   - achieve CVP of >8 mmHg
   - achieve Scvo2 of >70 %.

14.8.2 Sepsis Resuscitation Bundles (24-h Bundles)

1. Low-dose steroids administered for septic shock in accordance with a standardized ICU policy
2. Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy
3. Glucose control maintained greater than lower limit of normal but <150 mg/Dl (8.3 mmol/L)
4. Inspiratory plateau pressures maintained <30 cm H_2O for mechanically ventilated patients
5. Selective Digestive Decontamination (SDD).

14.9 Human Recombinant Activated Protein C (hrAPC): The Mysterious and Intricate Success

In a randomized double-blind, placebo-controlled, multicenter trial (PROWESS study) were enrolled a total of 1,690 patients (840 in the placebo group and 850 in the drotrecogin alfa activated group) [35].

Patients with systemic inflammation and organ failure were enrolled and assigned to receive an intravenous infusion of either placebo or drotrecogin alfa activated (24 μg/kg of body weight per hour) for a total duration of 96 h. The

primary end point was death from any cause and was assessed 28 days after the start of the infusion. Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis [36].

Randomly enrolled adults patients with severe sepsis and a low risk of death (APACHE <25 or single organ failure) assigned to receive an intravenous infusion of DrotAA (24 μg/kg of body weight per hour) or 96 h in a double-blind, placebo-controlled, multicenter trial. The prospectively defined primary end point was death from any cause and was assessed 28 days after the start of infusion. In-hospital mortality within 90 days after the start of the infusion was measured, and safety information collected.

In the study managed by Abraham et al. [37] were enrolled 2,640 patients and collected data on 2,613 (1,297 in the placebo group and 1,316 in the DrotAA group) at the 28-day follow-up. There were no statistically significant differences between the placebo group and the DrotAA group in 28-day mortality (17 % in the placebo group vs. 18.5 % in the DrotAA group), or in-hospital mortality (20.5 vs. 20.6). The rate of serious bleeding was greater in the DrotAA group versus placebo (2.4 % vs. 1.2 %) during both the infusion and the 28-day study period (3.9 % vs. 2.2 %).

The conclusion of Abraham et al. were that in the absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHEII score less than 25.3.

Contrastingly, Zambon et al. [38] reported interesting data to implement *Surviving Sepsis* Campaign Guidelines for Severe Sepsis and Septic Shock, we briefly report the core of their study.

Purpose—The aim of this study is to evaluate the feasibility of applying sepsis bundles in the ICU and their effect on outcomes.

Method—In this prospective, observational study in a 31-bed capacity department of intensive care, we measured the time taken to perform sepsis bundle intervention in 69 consecutive patients with severe sepsis or septic shock.

Results—Compliance with the 6-h bundle was obtained in 44 (72 %) of 61 patients; these patients had a lower mortality rate (16 % vs. 41 %, $P = 0.04$) and shorter ICU stay (median range), 5(3–10) versus (9 (6–19) days, $P = 0.01$). Compliance with the 24-h bundle was obtained in 30 (67 %) of 44 eligible patients. The mortality rate and duration of ICU were not significantly lower in the 24-h compliant as compared with noncompliant group (23 % vs. 33 % and 6 (4–11) versus 9 (6–25) days, respectively; P value is not significant). Patients who were compliant with the 24 h sepsis bundle after only 12 h had a lower mortality rate (10 vs. 39 %, $P = 0.036$) and shorter stay 6 (4–10) versus 9 (6–259 days, $P = 0.055$) than those who were compliant after 24 h.

Conclusion—Correct application of the sepsis bundles was associated with reduced mortality and length of ICU stay. Earlier implementation of the 24-h management bundles could result in better outcome.

14.10 SDD for Prevention of Infections in the Time of Global Economic Recession

In 2003, De Jonge et al. reported the effects of selective decontamination of the digestive on patient's mortality in randomized control trials and acquisition of resistant bacteria in intensive care: a randomized controlled trials [39].

In Table 14.8 are reported other four interventions supported by only one trial, providing a grade B recommendation, SDD can be administered to all patient at risk of infection, whereas the other four can be administered to specific subsets of ICU patients. It is difficult to understand the reason for omission of SDD intervention in the Surviving Sepsis Campaign guidelines, despite several randomized international controlled trials and many metanalysis showing a significant reduction of infectious morbidity and mortality.

A major difference between the only parenteral antibiotic used and SDD is that enteral antibiotics also impact the flora of the oropharynx and gut, whereas systemic agents only treat the lungs, blood, and bladder.

Classification of infection

- Primary endogenous infection: Staphylococcus aureus pneumonia that develop in young adults at day 5 following trauma is an example of primary endogenous infection in previously healthy individual
- Secondary endogenous infections: in medical/surgical ICU patients, secondary endogenous infection may develop without preceding primary endogenous infection
- Exogenous Infections: typical examples are Acinetobacter lower airway infections following the use of contaminated ventilation equipment or cystitis caused by Serratia.

Table 14.8 Intensive care unit intervention that reduces mortality

Intervention	Relative risk	Absolute mortality reduction % (95 %CI)	No. needed to treat
	(95 %CI)		
Low tidal volume [40]	0.78(0.65–0.93)	8.8(2.4–15.3)	11
Activated protein C [35]	0.80(0.69–0.94)	6.1(1.9–10.4)	16
Intensive insulin [41]	0.44(0.36–0.81)	3.7(1.3–6)	27
Steroids [42]	0.90(0.74–1.09)	6.4(4.8–17.6)	16
Selective	0.65(0.49–0.85)	8.1(3.1–12)	12
Decontamination [39]			

- The predilection for the tracheal site by Pseudomonas and Serratia species may be related to the chronic inflammation of the lower airways associated with tracheostomy.
- Only parenteral antimicrobials control primary endogenous infections
- Topical antimicrobials have been shown to control secondary endogenous infections
- High level of hygiene is essential to control exogenous infections.

Pneumonia is the major infection problem in the ICU patients, both on admission and during ICU stay. The diagnosis of ventilator-associated pneumonia is difficult; clinical features are not specific because infectious and noninfectious process may cause new lung infiltrates, fever, purulent sputum and/or leukocytosis. Treatment requires a diagnostic work-up and lack of diagnosis is a frequent cause of treatment failure.

Clinical diagnosis only:

- presence of a new or progressive pulmonary infiltrate on chest X-ray for >48 h
- Fever >38.5 °C
- Leucocytosis (WBC >12,000/ml or leucopenia <4,000/ml
- Purulent endotracheal aspirate evaluated with quantitative cultures at a threshold of >100,000 colony-forming units/ml or
- Microbiologically proven

14.10.1 Combination Therapy and Antibiotic Resistance

More than 75 % of patients admitted in ICU receive at least one antibiotic during their stay. The emergence of multiresistant bacteria is related to excessive antimicrobial use. Thus strategies, like de-escalation, which maximize the chance of providing appropriate antimicrobial therapy and minimise the risk of development of bacterial resistance, need to be encouraged.

The need for prompt initiation of appropriate antimicrobial therapy is emphasized for three clinical phenomena:

- Sepsis due to a presumed bloodstream infections (BSIs)
- Pneumonia
- Intra-abdominal infections.

Empirical antimicrobial therapy may also be required for selected infections, like meningitis or endocarditis or for a specific population

- In most ICU patients, immune responses are impaired, and defences against lower respiratory tract infections are compromised by the presence of the endotracheal tube, suppression of normal airway clearance mechamisms, and aspiration of upper respiratory and gastrointestinal tract secretion.

No more than 48 h is necessary to start the targeted antibiotic therapy depending on the cultures obtained from the microbiological monitoring accompanied by the relative antibiograms and MIC.

In the critically ill patients with severe homeostasis disorders, many different factors are involved in the pathophysiology of bacteria and endotoxin translocation, either in conditions of anatomically intact bowel barrier or in conditions of altered intestinal mucosa [43].

Preventing bacterial translocation can be attained both by improving intestinal function and the host defense mechanism. Therapies against translocation include selective decontamination of the digestive tract (SDD) to increase oxygen delivery and avoid hypoperfusion.

The rationale for the use of SDD is that lung infections in critically-ill patients may be caused by bacteria located in the oropharynx (and intestine). The use of enteral antimicrobial therapy associated with early parenteral administration of antibiotic agents may improve survival in critically ill patients and lead to a significant reduction in infections caused by Gram-negative germs [43, 44].

In particular SDD significantly reduce overall BSIs, Gram-negative BSI, and overall mortality, without affecting Gram-positive BSI [45].

Enteral use of antibiotics with topical applications of non absorbable antimicrobial agents mixtures, associated with high levels of hygiene and surveillance cultures proved effective for the prevention of endogenous secondary infections. The full protocol of systemic SDD reduces mortality rates in critically ill patients, particularly when successful decontamination is achieved [46].

Gut overgrowth is the pathophysiological event in the critically ill requiring intensive care, and it is related to the risk of developing a clinically important outcome; SDD controls overgrowth by achieving high antimicrobial concentrations effective against "normal" and "abnormal" potential pathogens rather than by selectivity [47].

SDD may be indicated in critically ill patients admitted in an ICU after surgery, traumas, burns, pancreatitis, liver dysfunction, and acute respiratory failure. In particular, high-risk surgical patients are treated orally with a PTA mixture (polymyxin E, tobramycin, and amphotericin B) and receive prophylactic parenteral antimicrobial therapy during anaesthesia induction. This approach seems to be encouraging and cost-effective, and in our view has not been included because of economic consideration that might lead to a radical change in the use of antibiotics, particularly in critically ill patients [48].

SDD significantly reduces the number of infections of the lower respiratory tract and bloodstream, multiple organ failure, and mortality. It also controls resistance, particularly when the full protocol of parenteral and enteral antimicrobials is used [49].

The ecology in intensive care changes continuously under the influence of many factors, involving patients, staff, and other antibiotics, so to attribute the development of ESBL to SDD alone is not good science. SDD using cefotaxime does result in an ecological shift toward a higher abnormal carriage rate of resistant AGNB. However, using surveillance samples, the evidence clearly shows that it also prevents transmission and *de novo* development of resistance because of the actions of polymyxin and tobramycin [50].

There is robust evidence from the literature which indicates that the full SDD regimen of parenteral and enteral antimicrobials significantly reduces morbidity, i.e., pneumonia and BSI, and mortality. Many meta-analyses have shown reductions in infection rates and mortality associated with the use of SDD or selective oropharyngeal decontamination (SOD) in ICUs [44, 46].

These interventions have not been widely implemented because of concerns that their use could lead to the development of antimicrobial resistance in pathogens; a systematic review and metanalysis [50] detected no relation between the use of SDD or SOD and the development of antimicrobial-resistance in pathogens in patients in the ICU, suggesting that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data. - Some researchers strongly indicated that the full protocol of SDD reduces mortality in critically ill patients, in particular when successful decontamination is obtained.

Selective oral decontamination and SDD should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; this infection control measure are supported by the SSC recommendations and these measure should be instituted in health care settings [34].

14.11 Translation Research

There is currently a significant and an unmet need for high quality translation research in critical care. The emergence of "-omics" technologies and sophisticated imaging techniques have resulted in a rapid growth of emerging biomarkers. Biomarkers would ideally provide early and reliable endpoints for proof of concept in clinical trials and inform clinical decision making through earlier and more precise diagnosis and risk stratification. Despite significant investment in basic science and time-consuming clinical trials, the majority of pharmacological interventions developed for critical illness have yet to translate into measurable clinical benefit. Future validation and qualification of emerging biomarkers allied to advances in pharmacogenomic profiling have the potential to provide valuable clinical information while accurately phenotyping patients enrolled in future clinical trials [51].

The successful translation of promising research findings from basic research laboratories into useful clinical products for the management of septic patients has proven to be a daunting challenge. The complexity and variability of the clinical entity referred to as sepsis makes it intrinsically difficult to model preclinical systems and predict efficacy of potentially useful, experimental, therapeutic agents.

Technological innovations in microarrays, microfluidics, and nanotechnology make it feasible to study the evolution of sepsis in small animal models in considerable detail. The recognized limitations of standard preclinical platforms used to study sepsis have lead to innovative approaches to study sepsis in silico, and in

more complex and clinically more valid ex vivo tissue perfusion models and animal systems. It is abundantly clear that sepsis researchers need to do a better job informing clinicians about the possible benefits and potential risks of new treatment interventions as they traverse the gap between the bench and the bedside [52].

Abnormalities in clinical parameters and routine laboratory tests are frequently detected at late stages of many diseases (too late to cure or to prevent life-threatening complications). Hence, earlier diagnostic and prognostic markers are needed for decision making and improving therapeutic outcome. In the present issue of Clinical Science, Rudiger and co-workers [53] report findings from a transcriptomic study, which revealed that changes in transcripts involved in amino-sugar metabolism, p53-dependent cell-cycle arrest, β-adrenergic signalling and intracellular calcium cycling in cardiac tissue of rats with early sepsis could discriminate survivors from nonsurvivors. These findings underscore the great potential of systems biology in translational medicine. However, further investigations should be done to make the benchside results more feasible for routine clinical practice [54].

Treatment strategies for critically ill patients can and should never be excluded from grading processes that classify the evidence and provide decision support for health care workers involved in the care of these patients. Along with grading the available evidence, implementing new therapies and strategies in daily practice is another important but frequently forgotten step in improving care for critically ill patients. Explanations for why some trials show benefit while other trials do not or even show harm include differences in the timing and the dose of the studied interventions, differences and heterogeneity of study populations and differences in trial protocols.

Potential factors that may hamper the implementation of new therapies and strategies include translational problems, potentially biased expert opinions, concerns about side-effects and costs and problems with the recognition of critically ill patients who might actually benefit from a new therapy or strategy.

Some authors discuss difficulties with grading the evidence for and the implementation of lung protective mechanical ventilation in acute respiratory distress syndrome, glucocorticosteroid therapy in refractory septic shock, glucocorticosteroid therapy in acute respiratory distress syndrome, goal-directed fluid therapy in shock, activated protein C in severe sepsis and intensive insulin therapy in critical illness [55].

In the era of evidence-based medicine, large, randomized, controlled, multicenter studies represent the “summit of evidence.” In contrast to specialties like cardiology, the majority of randomized, controlled trials in critical care medicine, however, have failed to demonstrate a survival benefit; notably, despite encouraging results from experimental and phase-II clinical studies.

The difficulty in translating our theoretical knowledge into successful multicenter randomized, controlled trials and subsequent treatment recommendations may represent one reason, why the mortality of septic shock still averages between 40 and 60 %, although our knowledge about the underlying pathophysiology has

considerably increased and international guidelines have widely been implemented. This article elucidates some of the difficulties in translating research from bench to bedside [56].

Given the panoply of system-level diseases that result from disordered inflammation, such as sepsis, atherosclerosis, cancer, and autoimmune disorders, understanding and characterizing the inflammatory response is a key target of biomedical research. Untangling the complex behavioral configurations associated with a process as ubiquitous as inflammation represents a prototype of the translational dilemma: the ability to translate mechanistic knowledge into effective therapeutics. A critical failure point in the current research environment is a throughput bottleneck at the level of evaluating hypotheses of mechanistic causality; these hypotheses represent the key step toward the application of knowledge for therapy development and design.

Addressing the translational dilemma will require utilizing the ever-increasing power of computers and computational modeling to increase the efficiency of the scientific method in the identification and evaluation of hypotheses of mechanistic causality. More specifically, knowledge representation. "Agent-based modeling" is an object-oriented, discrete-event, rule-based simulation method that is well suited for biomedical dynamic knowledge representation.

Agent-based modeling has been used in the study of inflammation at multiple scales. The ability of agent-based modeling to encompass multiple scales of biological process as well as spatial considerations, coupled with an intuitive modeling paradigm, suggest that this modeling framework is well suited for addressing the translational dilemma. This review describes agent-based modeling, gives examples of its applications in the study of inflammation, and introduces a proposed general expansion of the use of modeling and simulation to augment the generation and evaluation of knowledge by the biomedical research community at large [57].

Just some examples to focus the importance of translation research to solve the enigmatic dilemma about sepsis. Inflammation is a complex, multiscale biologic response to stress that is also required for repair and regeneration after injury. Despite the repository of detailed data about the cellular and molecular processes involved in inflammation, including some understanding of its pathophysiology, little progress has been made in treating the severe inflammatory syndrome of sepsis. To address the gap between basic science knowledge and therapy for sepsis, a community of biologists and physicians is using systems biology approaches in hopes of yielding basic insights into the biology of inflammation.

"Systems biology" is a discipline that combines experimental discovery with mathematical modeling to aid in the understanding of the dynamic global organization and function of a biologic system (cell to organ to organism). Vodovotz et al. propose the term translational systems biology for the application of similar tools and engineering principles to biologic systems with the primary goal of optimizing clinical practice. The Authors describe the efforts to use translational systems biology to develop an integrated framework to gain insight into the problem of acute inflammation. Progress in understanding inflammation using

translational systems biology tools highlights the promise of this multidisciplinary field. Future advances in understanding complex medical problems are highly dependent on methodological advances and integration of the computational systems biology community with biologists and clinicians [58].

Interlinked by a mutual cascade effect and driven by the host-pathogen interaction, microcirculatory and mitochondrial functions are impaired during sepsis. Mitochondrial respiration seems to evolve during the course of sepsis, demonstrating a change from reversible to irreversible inhibition. The spatiotemporal heterogeneity of microcirculatory and mitochondrial dysfunction suggests that these processes may be compartmentalized. Although a causal relationship between mitochondrial and microcirculatory dysfunction and organ failure in sepsis is supported by an increasing number of studies, adaptive processes have also emerged as part of microcirculatory and mitochondrial alterations.

Treatments for improving or preserving microcirculatory, mitochondrial function, or both seem to yield a better outcome in patients. Even though there is evidence that microcirculatory and mitochondrial dysfunction plays a role in the development of sepsis-induced organ failure, their interaction and respective contribution to the disease remains poorly understood. Future research is necessary to better define such relationships in order to identify therapeutic targets and refine treatment [59].

14.12 Perspective and Conclusion

Last but not least the increasing relevance of theragnostics should be mentioned. Theragnostic is best described as the use of biomarkers to identify patients, who are most likely to benefit from a certain intervention. In septic patients, procalcitonin represents an example for a biomarker that can be used to guide antibiotic treatment [60].

This approach of individualized medicine can be extended to pharmacogenomic biomarkers that give information about the probability of success for the individual compound, similar to the treatment of cancer. In this context, genetic differences between individuals will increasingly influence and potentially guide therapies in critical care. Concerning the use of AVP in septic shock patients, Nakada et al. reported that a specific genetic variation in leucyl/cystinyl aminopeptidase (=vasopressinase, the enzyme that metabolizes AVP) is associated with 28-day mortality in septic shock and with biologic effects on AVP clearance [61].

By determining this genetic variation, the probability of success of AVP therapy could be specified. In addition, dose selection of AVP might be guided by this knowledge. For example, if a patient has a genetically determined, increased AVP clearance, higher doses might be chosen for the treatment than for a patient with a low AVP clearance.

Clinical research reflects a mandatory prerequisite to translate basic research into clinical practice. While a lack of available qualified doctors to fill positions in hospitals as well as in the ambulant sector has prompted political decisions to counteract, Measures to prevent an increasing loss of academic profile have to tackle all aspects from undergraduate to postgraduate training to attract highly skilled doctors in sustainable structures to reflourish academic medicine. Cornerstones to achieve these goals involve establishing of structured graduate programs, acknowledgment of time spend in clinical research in residency programs, extra occupational opportunities to achieve dual qualification (e.g., Master programs in clinical research) as well as independent positions with inherent carrier perspectives in academic medicine for doctors interested in clinical and translational research [62].

In conclusion, improvement of translational research in sepsis and critical illness should consist of a bi-lateral approach. On the one hand, the clinical relevance of preclinical studies can be increased by the use of "high-fidelity" and "two-hit" animal models. On the other hand, RCTs should be designed to optimize time of study intervention, limit heterogeneity in patient characterization, standardize concomitant treatments, and investigate not a single but bundles of interventions. As a consequence, RCTs will probably become smaller in sample size, but hopefully will provide more valuable evidence for the benefit of our patients.

Knowledge has been enhanced by the identification of several pathophysiological mechanisms of sepsis, the availability of new diagnostic tools, the use of powerful antimicrobial agents, the awareness of the importance of source control, the development of new methods of organ function protection and support, particularly for the cardiovascular, respiratory and renal systems.

Despite the general improvements, the mortality rate of sepsis and organ dysfunction has remained essentially unchanged and unacceptable high. However, significant progress has been reported, and survival rates can still be improved by prevention and combined treatment. The use of evidence-based guidelines can significantly contribute to improve treatment standards and prevent the evolution of a multifactorial syndrome involving a high risk of death. Further, clinical trials are needed to understand the various mechanisms activated in sepsis, the biohumoral interactions,the predisposing conditions (age, infection site, co-morbidities, gender, genotype, and mediators) and the role of combined therapy.

Sepsis involves a complex interaction of innumerable factors, some of which may be difficult to identify, and that developing a definitive, targeted treatment is very difficult. The diagnosis of sepsis is still a major challenge because its clinical signs (tachycardia, tachypnoea, leukocytosis or leukopenia, and hypothermia or hyperthermia) are very aspecific (blood cultures in septic patient may be positive only in approximately 30–40 % of patients) and it is a complex multifactorial syndrome.

Sepsis is complicated especially to threated, all thanks to the dynamicity of the pathological events and the difficulties in capturing the specific time frame. The infection diagnosis is therefore a node of vital importance that starts from the

understanding, the clinical history and the objective examination, the history of invasive procedure and surgical history.

The application of basic principles of source control, and the EGDT aimed at normalizing hemodynamic parameters and reversing global tissue hypoxia in the pre-ICU period for severe sepsis and septic shock patients significantly decreases morbidity and mortality. The studies support that improving morbidity and mortality heavily depends on early recognition and treatment of high risk patients. Mortality may be reduced by focusing on early diagnosis, targeted management and standardization of the care process.

Together with advances in the availability of data and their quality (related to the increasing of computer power), the information collected with the scoring system combined with dynamic information should predict the outcomes and follow the physiology-pathophysiology of the patients as it is changing; this is the challenge for outcome research.

The future management of sepsis will most likely involve therapies directed at newer inflammatory targets (RAGE, HMGB-1). Future studies examining the pathogenic mechanisms or novel therapies for severe sepsis and septic shock should include lactate clearance as a measure of prognosis and therapeutic responses [63].

There are numerous obstacles that stand in the way of translating research into bedside practice, knowledge transfer in medicine remains a difficult and perplexing challenge first, especially in critical care, clinicians are conservative by nature.

Common experience demonstrated no significant decrease in the incidence of fungal infections in critically ill patients receiving selective decontamination of the digestive tract (SDD) was observed between those receiving enteral and total parenteral nutrition. SDD significantly reduced overall bloodstream, gram-negative BSIs and overall mortality, without affecting gram-positive BSIs. The full protocol of SDD reduces mortality in critically ill patients, in particular when successful decontamination is obtained.

Sepsis and septic shock are associated with substantial consumption of health care resources. The burden of sepsis on health care is significant; the sepsis evolution and organ dysfunction are still an enigmatic topic. The cost for hospital treatment in the USA is 14.6 Billion USD [www.world-sepsis-day.org]. Clinicians are challenged to manage this disease in an aging population with multiple comorbidities, relative immunosuppression, and a changing pattern of causative microorganisms. Furthermore, the incidence of sepsis is increasing and will continue to do so as the population ages.

An increasing challenge to our health system related to increasing number of elder patients, new live-saving technologies, invasive techniques and measures, nosocomial infections, community-acquired infections, resistance to antibiotics. Future clinical trials will have to focus on both treatment efficacy, the cost of experimental therapeutic approaches and ultimately a better outcome and quality of life for patients suffering of severe infections, sepsis and organ(s) failure.

Appendix from Surviving Sepsis Campaign 2013

	Bundles 2012	Grade
	Initial Resuscitation and Infection Issues	
Initial Resuscitation		
1	Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L) Goals during the first 6 h of resuscitation: a) Central venous pressure 8–12 mm Hg b) Mean arterial pressure (MAP) ≥65 mm Hg c) Urine output ≥0.5 mL/kg/h d) Central venous (superior vena cava) or mixed venous oxygen saturation 70 or 65 %, respectively	1C
2	In patients with elevated lactate levels targeting resuscitation to normalize lactate	2C
Screening for Sepsis and Performance Improvement		
1	Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy	1C
2	Hospital–based performance improvement efforts in severe sepsis	UG
	Diagnosis	
1	Cultures as clinically appropriate before antimicrobial therapy if no significant delay (>45 min) in the start of antimicrobial(s)	1C
	At least two sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 h) inserted	1C
2	Use of the 1,3 beta-D-glucan assay and mannan and anti-mannan antibody assays if available, and invasive candidiasis is in differential diagnosis of cause of infection	2B 2C
	Imaging studies performed promptly to confirm a potential source of infection	UG
	Antimicrobial Therapy	
1	Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock	1B
	Administration of effective intravenous antimicrobials within the first hour of recognition of severe sepsis without septic shock	1C

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	Bundles 2012	Grade
2a	Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis	1B
2b	Antimicrobial regimen should be reassessed daily for potential deescalation	1B
3	Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection	2C
4a	Combination empirical therapy for neutropenic patients with severe sepsis	2B
	Combination empirical therapy for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp.	2B
	Combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone for patients with severe infections associated with respiratory failure and septic shock, for *P. aeruginosa* bacteremia	2B
	A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections	2B
4b	Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known	2B
5	Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia	2C
6	Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin	Grade 2C
7	Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause	UG
Source Control		
1	A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 h after the diagnosis is made, if feasible	1C
2	When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred	2B
3	When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess) (UG)	UG
4	If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG)	UG

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	Bundles 2012	Grade
Infection Prevention		
1a	Selective oral decontamination and SDD should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; this infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective	2B
1b	Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis	2B
Fluid Therapy of Severe Sepsis		
1	Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock	1B
2	Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock	1B
3	Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids	2C
4	Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients	1C
5	Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables	UG
Vasopressors		
1	Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg	1C
2	Norepinephrine as the first choice vasopressor	1B
3	Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure	2B
4	Vasopressin 0.03 units/min can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage	UG
5	Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03–0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents)	UG
6	Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia)	2C

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	Bundles 2012	Grade
7	Phenylephrine is not recommended in the treatment of septic shock except in circumstances where: (a) norepinephrine is associated with serious arrhythmias (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target	1C
8	Low-dose dopamine should not be used for renal protection	1A
9	All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG)	
Inotropic Therapy		
1	A trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP	1C
2	Not using a strategy to increase cardiac index to predetermined supranormal levels	1B
Corticosteroids		
1	Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day	2C
2	Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone	2B
3	In treated patients hydrocortisone tapered when vasopressors are no longer required	2D
4	Corticosteroids not be administered for the treatment of sepsis in the absence of shock	1D
5	When hydrocortisone is given, use continuous flow	2D
Blood Product Administration		
1	Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease, we recommend that red blood cell transfusion occur only when hemoglobin concentration decreases to $<$7.0 g/dL to target a hemoglobin concentration of 7.0–9.0 g/dL in adults	1B
2	Not using erythropoietin as a specific treatment of anemia associated with severe sepsis	1B
3	Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures	2D

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	Bundles 2012	Grade
4	Not using antithrombin for the treatment of severe sepsis and septic shock	1B
5	In patients with severe sepsis, administer platelets prophylactically when counts are <10,000/mm^3 (10 × 109/L) in the absence of apparent bleeding. We suggest prophylactic platelet transfusion when counts are <20,000/mm^3 (20 × 109/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥50,000/mm^3 [50 × 109/L]) are advised for active bleeding, surgery, or invasive procedures	2D
Immunoglobulins		
	Not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock	2B
Selenium		
	Not using intravenous selenium for the treatment of severe sepsis	2C
History of Recommendations Regarding Use of rhAPC		
	The specific mechanisms by which drotrecogin alfa (activated) exerts its effect on survival in patients with severe sepsis are controversial, not completely understood and the evolution of SSC RECOMENDATIONS not recommended the use of rhAPC	
Mechanical Ventilation of Sepsis-Induced ARDS		
1	Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced ARDS (vs. 12 mL/kg)	1A
2	Plateau pressures be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflated lung be ≤30 cm H2O	1B
3	Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma)	1B
4	Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis-induced moderate or severe ARDS	2C
5	Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia	2C
6	Prone positioning be used in sepsis-induced ARDS patients with a Pao_2/Fio_2 ratio ≤100 mm Hg in facilities that have experience with such practices	2B
7	That mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30–45° to limit aspiration risk and to prevent the development of ventilator-associated pneumonia	1B

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	Bundles 2012	Grade
8	That noninvasive mask ventilation (NIV) be used in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks	2B
9	That a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria:	1A
	(a) arousable	
	(b) hemodynamically stable (without vasopressor agents)	
	(c) no new potentially serious conditions	
	(d) low ventilatory and end-expiratory pressure requirements	
	(e) low Fio2 requirements which can be met safely delivered with a face mask or nasal cannula	
	If the spontaneous breathing trial is successful, consideration should be given for extubation	
10	Against the routine use of the pulmonary artery catheter for patients with sepsis induced ARDS	1A
11	A conservative rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion	1C
12	In the absence of specific indications such as bronchospasm, not using beta 2-agonists for treatment of sepsis-induced ARDS	1B
Sedation, Analgesia, and Neuromuscular Blockade in Sepsis		
1	Continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints	1B
2	Neuromuscular blocking agents (NMBAs) be avoided if possible in the septic patient *without ARDS* due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used	1C
3	A short course of NMBA of not greater than 48 h for patients *with* early sepsis-induced ARDS and a PaO_2/Fio_2 <150 mm Hg	2C
Glucose Control		
1	A protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose ≤180 mg/dL rather than an upper target blood glucose ≤110 mg/dL	1A
2	Blood glucose values be monitored every 1–2 h until glucose values and insulin infusion rates are stable and then every 4 h thereafter	1C

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	Bundles 2012		Grade
3	Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values		UG
Renal Replacement Therapy			
1	Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure		2B
2	Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients		2D
Bicarbonate Therapy			
	Not using sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH $\geq$ 7.15		2B
Deep Vein Thrombosis Prophylaxis			
1	Patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) with daily subcutaneous low-molecular weight heparin (LMWH)		1B
		(a) versus twice daily UFH	1B
		(b) versus three times daily UFH	2C
	If creatinine clearance is < 30 mL/min, use	(a) dalteparin	1A
		(b) another form of LMWH that has a low degree of renal metabolism	2C
		(c) UFH	1A
2	Patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible		2C
3	Septic patients who have a contraindication for heparin use (e.g., thrombocytopenia, severe coagulopathy, active bleeding, and recent intracerebral hemorrhage)		
	a) not receive pharmacoprophylaxis		1B
	b) receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices, unless contraindicated.		2C
	c) When the risk decreases start pharmacoprophylaxis		2C
Stress Ulcer Prophylaxis			
1	Stress ulcer prophylaxis using H2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors		1B
2	When stress ulcer prophylaxis is used, proton pump inhibitors rather than H2RA		2D
3	Patients without risk factors do not receive prophylaxis		2B

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	Bundles 2012	Grade
Nutrition		
1	Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 h after a diagnosis of severe sepsis/septic shock	2C
2	Avoid mandatory full caloric feeding in the first week but rather suggest low dose feeding (e.g., up to 500 calories per day), advancing only as tolerated	2B
3	Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock	2B
4	Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis	2C
Setting Goals of Care		
1	Discuss goals of care and prognosis with patients and families	1B
2	Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate	1B
3	Address goals of care as early as feasible, but no later than within 72 h of ICU admission	2C

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Immunoglobulin as Adjunctive Therapy in Sepsis

15

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Abbreviations

SSC	Surviving Sepsis Campaign
ICU	Intensive Care Unit
SIRS	Systemic Inflammatory Response Syndrome
IgG/IgM	Immunoglobulin G/M
IgGAM	Immunoglobulin IgM enriched
SSP	Sepsis Stewardship Program
SOFA	Sequential Organ Failure Assessment
SAPS	Simplified Acute Physiology Score
RCT	Randomized Controlled Trial
CVP	Central Venous Pressure
$ScvO_2$	Central Venous Oxygen Saturation
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
rhAPC	recombinant human Activated C Protein

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15.1 Introduction

Sepsis is a syndrome characterized by a complex and multifaceted inflammatory host response to infection that may lead to rapid onset of acute organ failure and death. Severe sepsis may account up to 20 % of ICUs admissions and is the leading cause of death in noncardiac ICUs. In Italian intensive care units (ICU), the mortality rate of patients admitted with septic shock is still above 50 % and has not varied significantly in the past five years [1]. This high mortality rate is attributable to several factors, including difficulties in the early identification of septic patients, time for microbiological diagnosis, limited resources and the possible incorrect application of treatments proposed by the guidelines [2, 3].

Various experiences indicated that the application of evidence-based guidelines and the sepsis bundles strategy is associated with an improvement in patient's outcome. However, whether this improvement is due to specific treatments rather than bundle(s) application is still matter of debate [4]. Indeed, in the recent edition of the Surviving Sepsis Campaign Guidelines [3] the classical 6 and 24 h bundles strategy has been simplified and includes only indications for severity assessment, microbiological diagnosis, antibiotic therapy and resuscitation for patients with shock.

In addition to the interventions suggested by the SSC, other therapeutic options have been proposed and tested on patients with severe sepsis and septic shock. The guidelines by the German Sepsis Society [5] included as possible effective therapies in patients with severe sepsis:

(i) the use of albumin for volume therapy (recommendation level E, evidence level V);
(ii) therapy with epinephrine, phosphodiesterase inhibitors or levosimendan in patients with ventricular function impairment despite the administration of dobutamine (E, V);
(iii) the use of selenium (C, Ia); and
(iv) the use of IgM-enriched immunoglobulin preparation (IgM) (C, Ia).

15.2 The Rationale for the Use of Immunoglobulin in Sepsis

Severe sepsis is often associated with a decrease in immunoglobulin plasma levels (Ig) and patients with low Ig had a significantly longer duration of shock and a higher incidence of severe lung injury [6]. Indeed, only a transient hypogammaglobulinaemia not related to prognosis has been also reported in patients with severe sepsis lasting <48 h [7]. The reasons for the low Ig levels observed in sepsis (i.e. extravascular distribution, increased consumption, decreased production) and the Ig temporal course are still uncertain and future studies are needed to get a better understanding of the role of Ig decrease in patients with sepsis.

In sepsis, Ig can enhance the opsonisation of antigens, inhibit complement activation [8], neutralise endotoxin and even superantigens and protect the organism from endotoxin liberation following the administration of antibiotics [9]. Ig preparations, in particular IgM-enriched preparations, contain antibodies against lipopolysaccharides of Escherichia coli, Pseudomonas aeruginosa and Klebsiella spp. [10]. Ig interfere with many other aspects of the host response and are currently used for modulating excessive immune response in a wide range of diseases (e.g. Thrombotic Thrombocytopenic Purpura, Guillan-Barrè Syndrome, Kawasaky disease, demyelinising diseases). Therefore, in septic patients the adjunctive therapy with Ig may increase/restore the clearance of bacteria and toxins, facilitate the cellular immune-response and modulate the inflammatory host response processes [8, 11, 12].

15.3 Immunoglobulin Preparations

The conventional intravenous immunoglobulin preparation is a blood product prepared from a pool of more than 1,000 donors, thus providing a broad spectrum of opsonic and neutralising IgG antibodies against a variety of microbial antigens and multiple epitopes that may vary as a function of differences in the local pathogen ecology of donor exposure. Only one product contains IgM and IgA in the preparation (Pentaglobin, Biotest, Germany), with a relative composition of 76 % IgG, 12 % IgA and 12 % IgM. Compared to the traditional IgG preparation, the IgM enriched preparation better represents the composition of human plasma (Table 15.1) and contains antibodies against a wide range of different bacterial epitopes, that are well represented in the hospital epidemiology of infection, especially in Gram-negative infections [10, 13]. Moreover, IgM is the first class of antibodies involved in the host response to infection and its pentameric structure is more efficient at neutralizing toxins and in the bacterial agglutination compared with IgG.

15.4 IgM Enriched Immunoglobulin in Sepsis: Clinical Evidence and Practice

The effects of IgM preparation in patients with severe sepsis have been investigated since the early 1990s. Schedel et al. [14] reported a significant mortality reduction (4 % in the treatment group versus 32 % in the control group) due to the

Table 15.1 Composition of different preparation despite human serum

	IgG (%)	IgM (%)	IgA (%)
Human serum	80	7	13
IgM enriched preparation	76	12	12
Traditional intravenous IgG preparation	>97	traces	<3

use of IgM preparation in 55 medical patients with Gram-negative septic shock and high endotoxin levels. Other studies on mixed medical/surgical populations [15, 16] reported a mortality reduction in treated patients. A perspective multicentre trial evaluated the efficacy of the IgM preparation in surgical patients with septic shock by abdominal infection. The use of immunoglobulins in addition to antibiotic therapy was associated with a significant mortality reduction in the subgroup of patients who received adequate antibiotic therapy [17]. Indeed, a study showed that no benefit comes from the immunoglobulin therapy in neutropenic patients with low sepsis grade and low risk of death [18].

Although there are issues regarding the methodological quality of the available evidence, various meta-analyses [19–21] and a Cochrane review [22] indicate that adjunctive treatment with intravenous immunoglobulin (IgG), and particularly with the IgM-enriched preparation, may have a beneficial effect on patients with severe sepsis (Table 15.2). Nevertheless, the latest edition of SSC guidelines [3] suggests not using intravenous Ig in patients with severe sepsis or septic shock (grade 2B). This weak recommendation is supported by the negative results of one large multicentre randomised control trial [23] on septic adults treated with polyclonal IgG and by the methodological limitations of the trials reporting benefit from the use IgM enriched preparation.

In our clinical protocol for the ICU management of adult patient with septic shock, therapy with IgM-enriched preparation (at the dosage of 250 mg/kg per day for 3 consecutive days) was included as part of the 24 h management bundle since 2008. Due to an initial low adherence to protocol application, therapy with IgM enriched preparation was properly used in around 50 % of patients with septic shock only. Despite similar SOFA and SAPS II scores and sepsis bundles compliance, the 30-day mortality was lower ($p < 0.05$) in treated (41 %) than in

Table 15.2 Meta-analysis: efficacy of the immunoglobulin therapy in severe sepsis

	Studies; n randomized controlled trials; n patients (Treated/Control)	Mortality Odds Ratio (95 %CI)
Turgeon et al. [19]	All; 20RTCs; 1332/1289	0.74 (0,62-0,89)
	Blinded; 7RCTs; 465/431	0.61 (0,40-0,93)
	High Q; 3RCTs; 64/65	0.56 (0,31-1,01)
Laupland et al. [21]	All; 14 RCTs; 744/706	0.66 (0,53-0,83)
	Blinded; 6 RCTs	0.77 (0,59-1,01)
	High Q; 4 RCTs	0.96 (0,71-1,31)
Kreymann [20]	All; 15 RCTs; 756/736	0.79 (0,69-0,90)
	High Q; 8 RCTs; 510/487	0.81 (0,69-0,84)
Alejandra et al. [22]	All; 17 RCTs; 1015/943	0.77 (0.68-0.87)
	IgM-enriched; 7 RCTs; 269/259	0.66 (0.51-0.85)

*only adults included

no-treated patients (62 %) [24]. In these patients the effects of IgGAM on muscular microcirculation by near infrared spectroscopy were also investigated, and preliminary data indicated that its use is related to an early recovering of muscular O_2 consumption and to a rapid improvement of endothelial reactivity [25].

The treatment with polyclonal intravenous IgM enriched immunoglobulins has been used for several years in several countries in spite of the absence of clear evidence or guidelines. However, there are still many unanswered questions regarding the efficacy and the correct use of the IgM preparation. Recently, Molnár et al., proposed a consensus document on the use of IgM preparation by using published data and unpublished audits (Table 15.3) [26].

As refers to the type of patients who could benefit more from the treatment, IgM-enriched preparation seems to be more useful in patients with persistent septic shock and more than 2 organ dysfunctions. In these patients the treatment has to be started as soon as possible and in any case it is not recommended 48 h after the onset of the shock [27]. Another important issue is to identify a specific subgroup of patients depending on the aetiology of the septic shock. The literature, in particular in the Rodriguez et al. trial [17], suggests that surgical patients that more frequently undergo Gram-negative infections could benefit more from the IgM-enriched preparation treatment. On the other hand, there are also many conditions related to

Table 15.3 Target population for treatment with IgM enriched preparation

Requirements	Comments and concepts	Reference
Severity	Persistence of septic shock or severe sepsis with >2 organ dysfunctions after initial resuscitation/treatment	Heintrich et al. Expert opinion
Timing	As early as possible. Best effects are expected if treatment is initiated within the first 8 h of sepsis	Berlot et al.
	Late start of treatment (48 h) is not recommended	Expert opinion
Target groups/subgroups with the highest benefit probability	Abdominal infections in surgical patients (peritonitis) presumably Gram-negative bacterial infections	Rodriguez et al.
	Meningococcal sepsis Toxic shock syndrome Overwhelming post splenectomy infection Necrotizing fasciitis	Expert opinion
Dosage (80 kg)	50 ml/h for the first 6 h (15 g), followed by 15 ml/h for 72 h (54 g), daily re-evaluation	Expert opinion
Exclusion criteria	Standing Do Not Resuscitation order or limitation of therapy, incurable metastatic malignant disease, neutropenia due to haematological malignancies and according to Summary Products Characteristics	Expert opinion

fulminant infections (listed in Table 15.3) that could really benefit. About the dosage prescription, high doses (250 mg/Kg/die) in continuous infusion (0.4 ml/Kg/hour) for at least three consecutive days seems to be the more effective dosage.

15.5 Conclusions

In spite of any advance in awareness of the physiopathological mechanisms, mortality in patients admitted to hospital with severe sepsis and septic shock is still very high. However, the number of therapeutic options for treatment of septic patients has been reducing day by day for several years because of negative clinical trials. In this light, the use of Ig, and in particular the IgM-enriched preparations as adjunctive therapy seems to be somewhat beneficial in specific septic populations. However, well-designed large multicentre studies are urgently needed to better evaluate the role of IgM therapy in patients with septic shock.

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Part VII
Cardiac Arrest: Optimization of Current Protocols

Determinants for More Efficient Defibrillation Waveforms

16

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16.1 Introduction

Defibrillation is an important link in the chain of survival. The most frequent initial rhythm in out-of-hospital-witnessed cardiac arrest (CA) is ventricular fibrillation (VF) and cardiopulmonary resuscitation (CPR) alone cannot fully resuscitate a patient of CA [1, 2]. Early defibrillation is critical to survival since the probability of successful defibrillation diminishes rapidly over time and VF tends to deteriorate to pulseless electrical activity or asystole within a few minutes [3–5].

Defibrillation is accomplished by delivering a high energy shock, which creates a large electric field throughout heart and simultaneously depolarizes a sufficient mass of excitable cells thereby restoring spontaneous circulation [6]. Although the efficacy and safety of defibrillation is steadily improving over the past several decades, severe side effects including both contractile and electrical dysfunction still exit in emergency medicine [7, 8]. Therefore, developing more efficient defibrillation waveforms which can reduce the energy required to terminate fibrillation while limiting the risk of shock-induced cardiac injury remains a subject of extensive research.

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16.2 Principle and Mechanism of Defibrillation

Understanding the basic principle and mechanism of defibrillation is essential for the development of more efficient defibrillation waveforms. The physiological mechanism of ventricular defibrillation has been extensively investigated for many decades [9]. Although many hypotheses have been proposed, the definite mechanism of defibrillation still remain debatable a century after its inception.

16.2.1 The Probabilistic Nature of Defibrillation

The defibrillation is a stochastic process since fibrillation has been described as chaotic asynchronous fractionated activity of the heart [10, 11]. Due to the distinct characteristic that defibrillation is probabilistic in nature, there is no discrete value for the shock strength (i.e., defibrillation threshold, DFT) to indicate that a shock strength at or above the DFT will always successfully defibrillate. Although the mechanism for the probabilistic nature of defibrillation remains unclear, both animal and clinical studies have shown that the probability of successful defibrillation is a function of energy/voltage/current which has a logistic or sigmoidal relationship [12]. Efficacy is usually defined by the ability of a shock to terminate an (induced) episode of VF and is typically measured as the number of successful shocks divided by the total number delivered. Defibrillation efficacy therefore can be represented by a dose response curve with a gradual transition from unsuccessful to successful shocks (Fig. 16.1). Factors improving the success of defibrillation like superior lead position, or improved waveforms design may change the shape of the curves as well as the DFT.

16.2.2 The Mechanism of Defibrillation

The total extinction hypothesis was proposed by Wiggers in 1940 [13]. This hypothesis, which focused on the termination of VF activation fronts by the shock, stated that the shock must depolarize all excitable tissues and stop all activation fronts present on the entire ventricles during fibrillation in order to obtain a

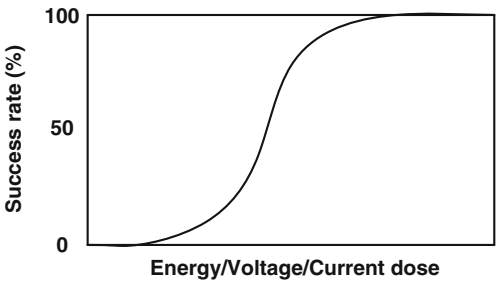

Fig. 16. 1 Dose response curve for ventricular defibrillation shocks

successful outcome. It also implied that, after a failed defibrillation, VF is reinitiated by any remaining activation front which is not halted by the shock.

The stimulatory theory of defibrillation, which postulated that defibrillation is achieved by directly stimulating and exciting the myocardium, was later refined into the critical mass hypothesis that shock does not need to stop all activation fronts on the entire heart for purpose of successful defibrillation, but only those occurring in the critical mass of the ventricles [6]. According to this hypothesis, failed defibrillation occurs because the shock failed to depolarize the critical amount of cardiac cells, allowing the remaining undisturbed cells to continue fibrillating, leading the whole ventricles back into VF. Experimentalists as well as theorists proposed that approximately 75–90 % critical mass of the myocardium needs to be directly defibrillated in order to fully terminate fibrillation [14, 15].

The findings that patterns of activation fronts following defibrillation shocks were always different from those before the shock in both successful and failed defibrillation led to the upper limit of vulnerability hypothesis [16, 17]. This hypothesis stated that in order to successfully defibrillate, a shock must have two of the following affects on the entire ventricles. First, the shock must stop all activation fronts present at the time when the shock is delivered by either directly activating the myocardium or by prolonging refractoriness of myocardium just ahead of these activation fronts. Second, the shock must not give rise to new activation fronts which could propagate away from the border of the directly excited region and reinitiate fibrillation.

Based on the findings that areas close to shocking electrodes produced virtual electrodes that either hyperpolarize or depolarize the surrounding tissue, the virtual electrode polarization hypothesis was proposed and has significantly advanced the understanding of defibrillation [18]. This hypothesis stated that if the optimal transmembrane potential gradient between the depolarized and hyperpolarized regions is met, activation fronts in the depolarized region can propagate into the hyperpolarized region, leading to reentry and eventually VF.

16.3 Determinants of Defibrillation Efficacy

Transthoracic defibrillation is achieved by applying a high-voltage pulse on patient's chest with the aid of two electrodes that may be either manual paddles or self-adhesive pads. The defibrillation efficacy is identified to be influenced by multiple factors, including time and location, heart and body weight, transthoracic impedance (TTI), drug therapy, capacitor size, delivered current and energy, waveform morphology and polarity, waveform duration, ratio of phase 2 to phase 1, paddle/pads size, electrodes placement, and sequential delivery of shocks [19–24].

16.3.1 Optimal Time for Defibrillation

The fundamental importance of early defibrillation as a major predictor of outcome in patients with VF has been known since portable direct current defibrillators were introduced in the 1960s. Early defibrillation is critical since survival rates decrease 7–10 % if no CPR is provided for every minute that passes between collapse and defibrillation. Clinical reports have clearly demonstrated that reducing the time to defibrillation in out-of-hospital CA would greatly improve survival to hospital discharge [2, 25–27]. Improved time to defibrillation can be achieved by reducing the time to recognize arrest, decreasing the time to initiate use of the defibrillator, and altering the design of defibrillator so that the shock can be delivered more quickly [28].

Although earlier defibrillation is greatly emphasized during CPR, it is increasingly clear that not all patients in VF benefit from being treated in the same manner, as the duration of VF is a major determinant of countershock outcome. There is evidence that when the interval between the onset of VF and the delivery of the first shock is less than 5 min, an immediate electrical shock may be successful [2, 29]. However, both animal and human studies demonstrated that when the duration of untreated VF exceeded 5 min, initial CPR with chest compression before delivery of a defibrillation attempt improved the likelihood of restoration of spontaneous circulation (ROSC) [30, 31]. On the other hand, repetitive unnecessary high energy defibrillation could damage the already precarious myocardium and cause severe postresuscitation myocardial dysfunction [32–34]. For these reasons, the ability to gain information concerning the metabolic state of the myocardium and to optimize the timing of defibrillation would be of enormous benefit in allowing therapy to be tailored to an individual heart. The optimal timing of defibrillation is usually determined through evaluating the probability of shock outcomes. If the attempted shock has a high likelihood of defibrillation success, an electrical shock should be prompted and delivered. Otherwise, unnecessary shocks should be avoided and alternate therapy such as CPR or medications, especially high quality chest compression, should be emphasized. For the purpose of optimizing the timing of defibrillation, both invasive and noninvasive hemodynamic measurements has been investigated, including coronary perfusion pressure (CPP), end-tidal CO2 (EtCO2), and characteristics of VF waveforms [35, 36].

16.3.2 Electrodes and Patient-Related Factors

Electrodes and the patient-electrode interface are important factors that affect the defibrillation outcome. The optimal selection and placement of defibrillation paddles/pads is one of the major determinants that affect the TTI, shock current density through the heart, and ultimately the defibrillation success rate [23]. An ideal anatomical placement of the defibrillation paddles/pads in the victim's chest is to maximize the amount of current delivered to the myocardium because only

4–5 % of the shocking energy actually reaches the heart. The increasingly widespread use of self-adhesive defibrillator pads, besides allowing for a continuous monitoring of high quality ECG trace and a quicker delivery of the shock with increased operator safety, also showed superiority in defibrillation efficacy compared with traditional hand-held electrode paddles in the management of prehospital VF [37]. However, inappropriate electrode placement is still not uncommon in the use of automatic external defibrillators (AEDs). For example, Heames et al. demonstrated that in only 22 % of instances, pads were placed within 5 cm from the position recommended by guidelines [38]. In another study performed by Lakhotia et al. [39], the correct paddle position was reported by only 17 % of the 1187 doctors surveyed. Electrode pad size is another important determinant of patient impedance and may contribute to the differences of reported TTI. In a clinical study, large self-adhesive defibrillation pads were found to be associated with a lower TTI and improved success rate [40].

Although clinical data demonstrated that the 4 different pad positions (anterolateral, anteroposterior, anterior-left infrascapular, and anterior-right infrascapular) were equally effective for the treatment of atrial and ventricular arrhythmias and any of the 4 pad positions was reasonable for defibrillation according to the Guidelines [41], Ristagno et al. [42] reported that anterior–posterior pads position was more efficient than anterior-lateral placement to terminate VF in a pediatric porcine model of short term CA.

16.3.3 Characteristics of Defibrillation Waveform

The waveform of a shock is the temporal pattern of its amplitude, measured by voltage or current. It interacts with cardiac electrical activity via its electric field, which is the instantaneous spatial derivative of shock voltage. The success or failure of defibrillation depends on the relationship between the predictable spatial and temporal characteristics of the electrical field and the chaotic spatial, as well as temporal characteristics of VF [43].

Since characteristics of defibrillation waveform are associated with defibrillation efficacy and affect the cardiac damage caused by a shock, multiple waveforms have been designed for clinical application since the first successful defibrillation performed with a shock. Figures 16.2 and 16.3 illustrated the morphology of commonly used monophasic and biphasic waveforms for external defibrillators. The earliest capacitive-discharge defibrillation waveforms, namely monophasic damped sinusoidal waveform, are not truncated. Schuder et al. [44] first reported that transthoracic defibrillation was much more effective with truncated waveforms compared to the damped sinusoidal one in animal study. Subsequently, the effect of truncation on defibrillation efficacy has been studied extensively. Gurvich was the first to demonstrate the superiority of the biphasic waveform over the monophasic waveform in dogs in 1967 [45]. Clinical data from both out-of-hospital and in-hospital studies indicated that lower energy biphasic waveform

shocks had higher success for termination of VF than monophasic waveform shocks [46–48]. Biphasic defibrillation waveforms have become the norm for external defibrillators in the past few years.

Defibrillation efficacy has been shown to be dependent on waveform duration for monophasic waveforms [49]. For biphasic waveforms, both first and second phases are shown to influence the defibrillation efficacy as well [21, 22]. The ideal duration of a biphasic waveform's first phase is the one with a phase duration as close as possible to the time constant of cardiac cell membrane. Biphasic waveforms with equal first and second phase durations and a total duration between 6 and 16 ms have been recognized as valid defibrillation waveforms [22]. A defibrillation waveform with a first phase duration longer than 10 ms, instead, has significantly worse defibrillation outcome [50]. The optimal defibrillation waveform duration has been thought to increase the shock efficacy with lesser requirements for energy and current delivered during the defibrillatory shock. In a recent study, Shan et al. [24] confirmed that the first phase duration played a main role on defibrillation success for a dual time constant biphasic waveform in a guinea pig model of VF. The intermediate first phase duration of 5 ms yielded the best defibrillation efficacy compared with shorter or longer first phase durations, while the different second phase duration did not affect defibrillation outcomes.

In an earlier clinical study, Natale et al. [51] reported that the waveform tilt had an impact on the defibrillation efficacy of biphasic shocks. In an attempt to improve defibrillating shock efficacy, many modifications therefore have been made to the traditional high tilt biphasic truncated exponential (BTE) waveform. Adjusting waveform tilt has attempted to reduce potential myocardial damage caused by defibrillating shocks by reducing voltages whilst maintaining efficacy. Both animal and clinical studies have shown that low tilt rectangular biphasic waveforms were more successful than higher tilt capacitor-based waveforms for the cardioversion of atrial fibrillation [52, 53]. More recently, Darragh et al. [54] reported that first shock and cumulative third shock success rates were improved and the energy required for VF treatment was reduced with the use of a low tilt biphasic waveform in CA patients.

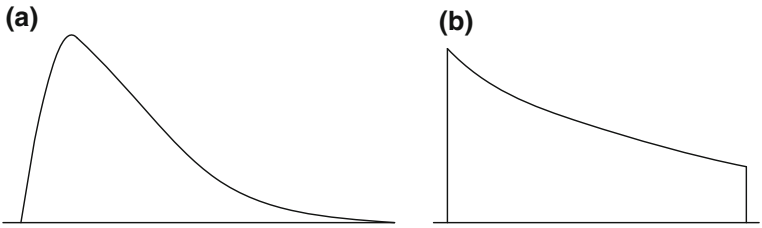

Fig. 16.2 Two types of monophasic waveforms. **a** Monophasic damped sinusoidal waveform. **b** Monophasic truncated exponential waveform

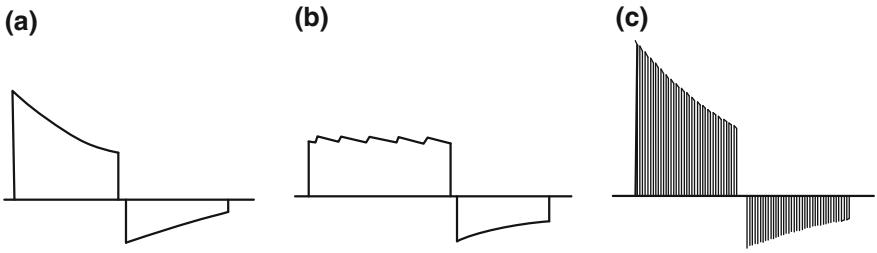

Fig. 16.3 Three types of biphasic waveforms. **a** Biphasic truncated exponential waveform. **b** Rectilinear biphasic waveform. **c** Pulsed biphasic waveform

Although it is accepted that defibrillation is accomplished by the passage of sufficient current through the heart, energy is still the only parameter clinically used for the selection of the therapeutic dose for current biphasic electrical shocks. With optimized waveform morphology and shock duration, the efficacy of defibrillation and risk of damage mainly depend on the delivered current and energy. However, the actual current flow is determined not only by the selected energy but also by the TTI of the patients. If the TTI is high, low energy may generate inadequate current to achieve defibrillation [55]. Current, which is less affected by the intra- and extracellular impedance, has been demonstrated to be a better indicator for the shock strength. Kerber et al. [56] showed that there was a positive correlation between peak current and shock success for both atrial and ventricular arrhythmias with monophasic shocks. Tang et al. [57] demonstrated that higher peak current was positively associated with improved survival when two different BTE waveforms were compared. Ristagno et al. [58] also proved that peak current was better than energy and voltage as a predictor of defibrillation outcome when rectilinear biphasic (RLB) and BTE waveforms were investigated in a short-term VF model of CA. Average current also has the advantage as a better measurement for the effectiveness of shock when waveforms with different shapes and equal durations were compared [59]. Since the concept of current-based defibrillation has been shown to be clinically feasible and effective, the transition in dose selection from energy-based defibrillation to current-based defibrillation will be promising.

16.4 Optimizing Biphasic Waveforms

Beginning with early experiments using high voltage shocks through large capacitor discharges across the closed chest, the search for the more effective defibrillation strategy is still ongoing. These developments enabling defibrillation with more efficient also permit further reductions in energy required for defibrillation. Ideally, optimization of defibrillation shocks should be based on, or at least guided by, a clear understanding of the mechanism of defibrillation. However, in practice, the search for optimal shock strategies has been largely empirical, via

testing of numerous defibrillator waveforms in animal experiments and clinical studies due to the existing conflicting theories.

16.4.1 More Efficient Biphasic Waveforms

Morphology of the waveform plays a major role in determining defibrillation outcome. Yamanouchi et al. [60] showed that DFT voltage and/or energy could be significantly lowered with the use of biphasic fully discharging capacitor waveforms (Fig. 16.4) compared with their corresponding monophasic waveforms. They also found that biphasic waveforms using two separate and fully discharging capacitors significantly decreased the energy required for defibrillation.

Earlier animal study demonstrated that a monophasic ascending ramp waveform has higher defibrillation efficacy compared with the descending ramp waveform [61]. Mathematical analysis based on charge burping hypothesis also showed that the theoretically optimal biphasic waveform was the one began at a non-zero percentage of the peak voltage and then rise in an exponential upward curve [62]. In a clinical study, Shorofsky et al. [63] compared the efficacy of ascending ramp waveform (Fig. 16.5) with a standard BTE waveform from implantable cardioverter-defibrillator (ICD) in 63 patients. The results proved that such a waveform can significantly reduce the DFT and were superior to BTE for defibrillation. In a recent animals study, the ascending ramp waveform was also

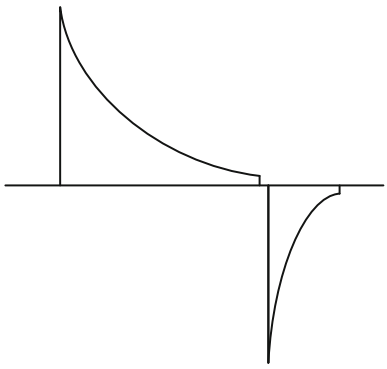

Fig. 16.4 Fully discharging exponential biphasic waveform (adapted from Ref. [60])

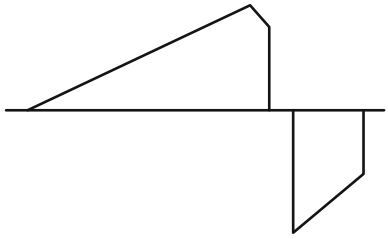

Fig. 16.5 Ascending ramp biphasic waveform (adapted from Ref. [62])

found to cause less troponin I release than the traditional BTE shocks in a pig model of short-term VF [64].

In another clinical trial, Seidl et al. [65] reported a significant reduction in DFT for a stepped waveform in comparison with a common used BTE waveform. As shown in Fig. 16.6, the stepped waveform is comprised of three parts using two capacitors in parallel and series: the first portion is positive with two capacitors in parallel, the second is positive with the capacitors in series, and the last portion is negative, also positive or negative with the capacitors in series.

16.4.2 Defibrillation Waveform Adjustment (Impedance Compensation)

The main determinants of intracardiac current flow during electric counter shock are the energy selected and TTI of the patient. The measured TTI, which includes the electrode–skin interface and the patient impedance, varies substantially among human subjects, ranging from 30 to 200 ohm in external defibrillators [47]. The development of methods to predict TTI in advance of a defibrillatory shock has been a significant aid, enabling novel techniques for defibrillation to emerge and closer examination of factors involved in determining the success or failure of counter shocks [55, 66]. The optimization of defibrillation waveforms therefore can be achieved by dynamically adjusting the delivered voltage/current, tilt, pulse duration, and waveform morphology based on the patient's TTI. The application of impedance compensation technique has been shown to be highly effective in terminating VF when patient TTI varies [66]. Three different impedance compensation strategies, namely current-based, energy-based, and voltage-based method are used by different external defibrillators. As shown in Fig. 16.7, the current-based method compensates for changes in TTI by increasing the voltage and delivering a near constant current with a fixed-duration shock. The energy-based method compensates for variability in TTI by delivering a constant energy with increased voltage and prolonged waveform duration (the total pulse duration of first and second phases). The voltage-based method, instead, maintains the

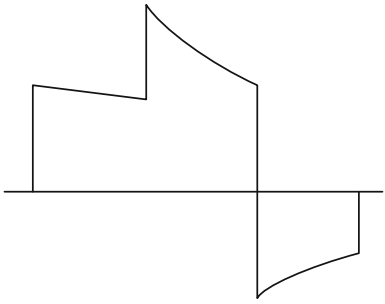

Fig. 16.6 Stepped waveform and predicted membrane response (adapted from Ref. [65])

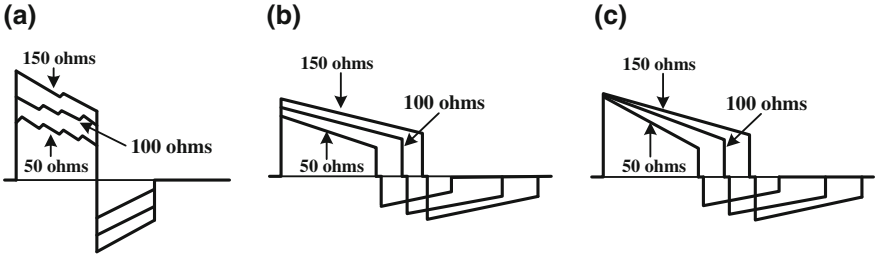

Fig. 16.7 Three different impedance compensation methods. **a** Current-based compensation. **b** Energy-based compensation. **c** Voltage-based compensation

voltage constant while prolongs the total duration of the shock waveform to compensate the increased TTI [58].

Although a significant improvement in success rate of shocks has been observed when the energy was automatically increased to compensate for higher TTI, but the defibrillation efficacy may differ since the waveform design and the impedance compensation method differ markedly among manufacturers. In a pig model of high impedance, the current-based compensation technique was demonstrated to be more effective than the duration-based and voltage-based compensation technique when the TTI was greater than the average [67].

Unlike external defibrillation, modern ICDs use constant tilt (50–70 %) biphasic waveforms. However, the theoretical tissue model-based estimates of phase 1 and phase 2 durations are considerably shorter than the pulse widths currently used in standard tilt ICDs [68]. A tuned waveform based on the model of membrane characteristics with a time constant of 3.5 ms, was developed [69]. According to this model, the optimal duration of tuned waveform is derived by the measured lead impedance and the device capacitance. For phase 1, the truncation point coincides with the peak membrane response. For phase 2, the duration ends with a membrane response near or just below zero. Recent clinical studies demonstrated that the energy and voltage DFTs were lowered with an ICD that used a tuned waveform compared to a standard constant tilt biphasic waveform [70–73]. However, the concept of the tuned waveform has not been tested on external defibrillations.

16.5 Research on More Efficient Waveforms

Although biphasic defibrillation is more efficient than monophasic defibrillation, researches for more efficient low energy defibrillation are continuing, such as multiple defibrillation waveforms and multiple (sequential) pulses shocks. These developments enabling defibrillation with less energy may permit further reductions in defibrillation caused myocardial injury.

16.5.1 Multiphasic Waveforms

Triphasic waveform (Fig. 16.8a), which is composed of three pulses with the polarity of the second pulse reversed (i.e., positive, negative, and positive), has been evaluated to have a high safety factor by Jones et al. [74]. In their study, the authors postulated that the first pulse of a triphasic waveform acted as a conditioning prepulse, the second pulse as an exciting or defibrillating pulse, and the third pulse as a healing postpulse, which ameliorated dysfunction caused by the first two pulses. On the other hand, the efficacy of triphasic waveform was found to depend on phase duration and electrode polarity. Triphasic transthoracic shocks composed of equal duration pulses were superior to biphasic shocks for VF termination at low energies [75, 76]. For open-chest defibrillation, Zhang et al. [77] proved that triphasic waveform shocks were superior to biphasic waveform shocks for VF termination at energy levels of 3–20 J and were as safe as biphasic shocks. Zhang et al. [78] also tested the efficacy of quadriphasic waveform (Fig. 16.8b) and found that equal duration quadriphasic waveform was superior to similar triphasic shocks for transthoracic defibrillation in animals with simulated high impedance.

16.5.2 Sequential or Multiple Pulse Shocks

Research into other waveforms such as sequential or multiple pulse shocks also yielded promising results. Kerber et al. [79] showed that sequential overlapping pulse shock waveforms with pulse 2 beginning and ending 2.5 ms after pulse 1 (Fig. 16.9) using two different pathways facilitate defibrillation compared with single pulse shocks of the same total energy in a canine model. This finding may arise from, at least in part, the changing orientation of the electrical vector during multiple pulse shock and directional sensitivity of myocytes to electric field stimulation.

Prompted by the widespread application of antitachycardia pacing for treatment of ventricular tachycardia, Li et al. [80] compared the efficacy of phase-independent multiple monophasic and biphasic shocks in a rabbit model chronic infarction. In contrast to single shock, a 5-pulse cardioversion approach was found to be more efficacious than biphasic shocks. Other studies also demonstrated that

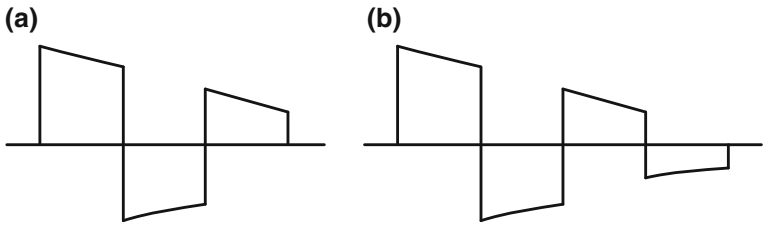

Fig. 16.8 Multiphasic waveforms. **a** Triaphasic waveform. **b** Quadriphasic waveform

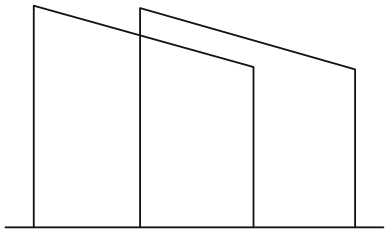

Fig. 16.9 Sequential overlapping pulse waveform consists of two truncated exponential waveform pulses (adapted from Ref. [79])

low voltage multiple-shock defibrillation was more efficient for the termination of atrial fibrillation compared with single shock [81, 82]. According to another recent animal study, the application of a sequence of low energy electrical filed pulse could significantly reduce the energy required for successful defibrillation by launching numerous propagating waves from many virtual electrodes across the heart [83]. These findings may provide new research perspectives toward alternative, life-saving low energy defibrillation techniques.

16.6 Conclusion

The evolution of defibrillation included significant work on optimization of the defibrillation waveform from its initial discovery. Earlier defibrillation studies primarily focused on AC defibrillation. Following the finding that significantly higher efficacy of DC defibrillation, defibrillation therapy evolution focused on DC shock defibrillation by optimizing the biphasic waveforms during the past several decades.

Recent research has identified areas of defibrillator design that may be of benefit if incorporated into mainstream commercially available devices. One example is the development of current-based defibrillation. Since current has been shown to be a better descriptor of dose selection and a better predictor of shock success in comparison with the energy, a microprocessor controlled current-based defibrillator which can automatically measures TTI and calculates the required energy may enable rapid delivery of an accurately calibrated preselected transthoracic current to patients. Another very important area for future improvement of defibrillation is the combination of shocks with cardiac pacing since it is known that pacing can influence and terminate reentrant or triggered arrhythmias. However, these approaches still merit further exploration on the mechanisms of fibrillation and defibrillation. It is anticipated that with more experimental and clinical experiments about the proposed methods are investigated, an increasing applications of the optimizing defibrillation waveform technologies in the medical fields will be observed.

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Post-Resuscitation Hypothermia and Monitoring

17

Tommaso Pellis, Filippo Sanfilippo, Andrea Roncarati and Vincenzo Mione

17.1 Introduction

In 2008, the International Liaison Committee on Resuscitation (ILCOR) published a consensus statement that officially acknowledged the existence of a *post-cardiac arrest syndrome* (PCAS) [1]. Negovsky was the first to understand the complexity of the period that follows cardiac arrest (CA) and resuscitation, and in 1972 he defined this state as post-resuscitation disease [2]. Now ILCOR clearly defines the epidemiology, pathophysiology, treatment, and even elements useful for prognostication of this syndrome [1]. With a bold step forward, ILCOR consensus statement provided physicians clear objectives that can be summarized in four key components to be addressed during in-hospital management of this syndrome: (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, (3) systemic response to ischemia and reperfusion, and (4) persistent precipitating pathology.

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The ILCOR consensus statement for the first time provides time phases of the PCAS to which correspond specific therapeutic goals [1]. The growing complexity of therapeutic options requires a clear understanding of the objectives and strategies to achieve each goal. This implicitly demands a hierarchic scale of priorities and careful monitoring which can be achieved only through standard operative procedures (SOPs). Similarly to the early goal directed therapy of the surviving sepsis campaign bundles, the post-arrest phases may be addressed by a resuscitation bundle in the immediate and early phase lasting from the first 20 min after restoration of spontaneous circulation (ROSC) to the first 6–12 h (Fig. 17.1). A subsequent management bundle addresses the intermediate phase lasting approximately until 72 h post-ROSC. The aim of these two bundles is to limit on-going injury and provide organ support. Prognosis, included as third bundle,

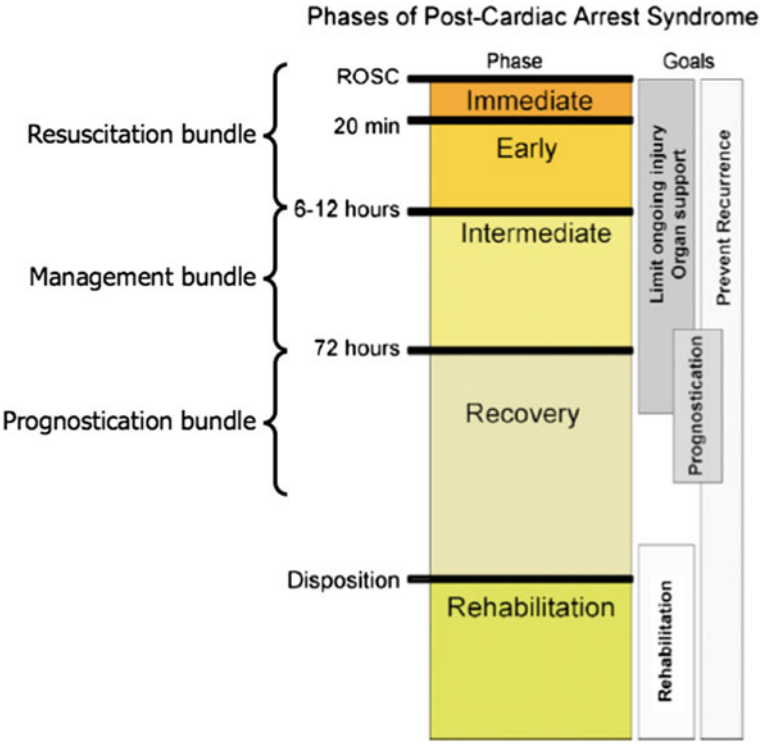

Fig. 17.1 Timeline, objectives and strategies with which to approach standard operative procedures for post-resuscitative care. Adapted from: Nolan JP et al., Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A scientific statement from the international liaison committee on resuscitation; the American heart association emergency cardiovascular care committee; the council on cardiovascular surgery and anesthesia; the council on cardiopulmonary, perioperative, and critical care; the council on clinical cardiology; the council on stroke. Resuscitation 2008;79(3):350–379

should take place no earlier than 3 days following ROSC. At all times, prevention of recurrence of CA is one of the top priorities.

Ultimately this consensus statement portrays a complex state in which hypothermia is only one facet of a broader therapeutic plan: *post-resuscitation care.*

Limiting on-going organ injury and providing organ support particularly to the cardiovascular, renal, pulmonary systems, as well as adopting neuro-protective strategies including therapeutic hypothermia (TH), requires not only intensive care but also intensive monitoring. Monitoring is inevitably associated to management, and not surprisingly five scientific societies decided to replace the term of TH with *target temperature management* [3]. Furthermore, a dedicated monitoring strategy is also necessary to ensure prompt diagnosis and aggressive therapy of epilepsy and myoclonus. In addition, monitoring tools are necessary to determine neurological prognosis in a multimodal manner, in the absence of a single tool with sufficiently high sensibility and specificity to discriminate positive and unfavorable recovery [4].

17.2 Target Temperature Management

Introduction of TH has revolutionized the treatment of CA as this is one of only three treatments that significantly improves survival and neurological outcome at hospital discharge [5, 6]. Along with cardiopulmonary resuscitation and defibrillation, only TH has been proven effective. To the contrary, advanced life support interventions including drugs and airway management do not impact on outcome [7].

If patient selection in multicenter trials on TH was limited to victims presenting in ventricular fibrillation or ventricular tachycardia (VF/VT), registries suggest an impressive improvement also in patients presenting with the "so-called" agonal or non-shockable rhythms [5, 8]. The Hypothermia Network Registry reports a 21 % survival with good neurological outcome in patients with asystole as first detected rhythm, and a similar rate (23 %) for those with pulseless electrical activity (PEA) [9]. The growing success of hypothermia has led ILCOR and resuscitation societies to officially extend its indications to non-shockable rhythms [7, 10]. For instance, the 2010 European Resuscitation Council (ERC) guidelines recommend to extend the use of therapeutic hypothermia also to comatose survivors of CA with non-shockable rhythms, following in-hospital arrest or for the pediatric population, even if the lower level of evidence for these classes of patients is acknowledged [7].

Although there are many postulated mechanisms of TH, this treatment is instituted to mitigate the anoxic brain injury that follows CA and resuscitation [1]. In patients remaining unconscious after ROSC—defined as that do not obey command—cooling to 32–34 °C for 24 h should be started as soon as possible. Induction of TH should not be delayed until hospital admission. Cooling can be safely and effectively started on the scene and during transportation. This can be easily achieved by simple and inexpensive means and taking advantage of the

impaired thermoregulation that follows ROSC. Cold (4 °C) IV crystalloids have been shown effective and safe even at rapid and large infusion rates such as 30 ml/kg over 30 min [11]. A recent French registry not only reaffirms the safety of IV fluids suggesting an unchanged incidence of pulmonary edema but also an overall reduced recurrence of CA [12]. Cold infusions can be easily stored in ambulances and combined with surface cooling methods, such as standard ice-packs or commercially available tools like the Emcool Pads®.

In the 7 years' experience of the emergency medical service (EMS) of the province of Pordenone (north-east Italy), cooling on the scene was performed in 56 patients. Hypothermia was initiated with straightforward and inexpensive means without delaying hospital admission; this tools included ice packs and other simple maneuvers to promote heat loss (i.e. turning off ambulance heating, opening the window, uncover patient as much as possible) and cold IV fluids. When comparing temperature at ICU admission with a population of 117 CA patients that were not cooled before ICU admission (including in-hospital CA), there was a significant reduction in core temperature if cooling was started in the out-of-hospital setting (34.7 ± 2.1 °C vs. 35.4 ± 1.3 °C, $p < 0.01$). This successful experience has led to a broader acceptance of out-of-hospital cooling and to modify the medical record used by EMS personnel in the entire Friuli Venezia-Giulia, the north-eastern region of Italy with a population of 1,200,000 and which includes Pordenone's province (Fig. 17.2).

Yet, there is currently no evidence that rapid cooling is associated with better outcome. To the contrary a report form 17 Italian ICUs suggest an increase in mortality if hypothermia is begun within 2 h of ROSC [13]. On the other side, animal data strongly support the benefit of prompt institution of hypothermia, with a marked reduction in infarct size, histological neuronal damage, and apoptosis. This apparent discrepancy can be explained if considering the degree and the extent of impaired thermoregulation as an indicator of the severity of post-resuscitation disease, and thereby of poor prognosis [14]. Moreover if the therapeutic action of hypothermia is considered as a continuum spectrum with higher intensities at lower temperatures, patients that do not achieve rapidly the target temperature (e.g., elevated BMI (Body Mass Index)) and that are then maintained for 24 h at 33 °C will be exposed to a greater cooling time and thus to a larger area under the curve of neuroprotection than those who achieve rapidly the target temperature. Based on these considerations and in keeping with current guidelines, cooling should be started as soon as possible [7]. It is worth reminding that this is an emergency treatment that is among the few of proven efficacy for CA patients and in particular the only one pertinent to the post-resuscitation phase. Moreover, induction of TH in the pre-hospital setting is not irreversible. If cooling is deemed inappropriate when reassessing the patient in the emergency department, it can be easily interrupted or reversed.

There are no absolute contraindications to attempt to mitigate post-CA brain injury [7, 15]. The pivotal trials on hypothermia included patients with cardiogenic out-of-hospital CA in VF/VT. Traumatic arrest and non-pharmacological bleeding

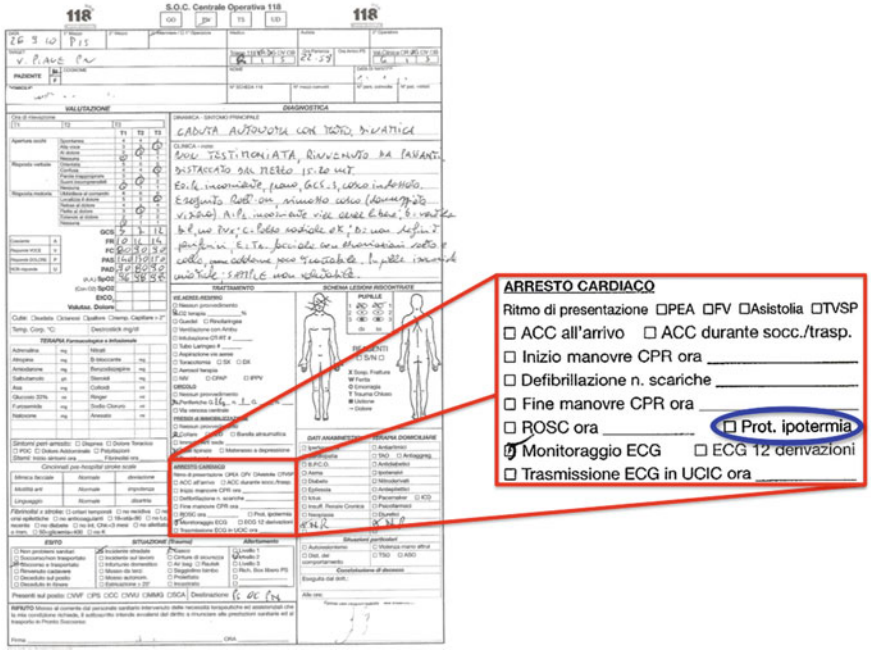

Fig. 17.2 Medical record of the emergency medical service in the Friuli Venezia Giulia region in the north-east of Italy. Hypothermia is contemplated among out-of-hospital interventions in cardiac arrest patients

diathesis were among exclusion criteria. In such patients for instance a careful risk/benefit assessment should be performed particularly when life-threatening bleeding has been treated or excluded.

The only real contraindications to the institution of post-CA cooling are those conditions in which an aggressive intensive care is deemed to be futile, such as dementia, pre-existing severe neurological impairment or terminal illness (not just limited to tumoral but including for instance neurodegenerative illness) [15].

Once assessed the appropriateness of intensive treatment, the "chain of cold" should not be interrupted even when performing diagnostic evaluations or therapeutic procedures such as CT-head scan, coronary angiography, or percutaneous coronary interventions (PCI). A recent Australian trial on out-of-hospital cooling (by means of cold IV fluids) was interrupted for futility after enrolling 234 patients. Despite an initial significant decrease in core temperature at hospital admission cooling was not immediately continued, thus allowing for patients to rewarm. Therefore, they achieved the target temperature with similar timespan as controls did.

17.3 Cooling Methods

Cooling can be achieved in an inexpensive fashion by the use of simple ice packs and/or wet towels. However, these methods may be more time consuming for nursing staff, result in greater temperature fluctuations and do not enable controlled rewarming [7].

Several commercially available devices ensure automatic temperature management both invasively and non-invasively. Such devices ensure not only to program 24 h cooling at 33 °C and to institute gradual and controlled rewarming (at 0.2–0.5 °C/h), but can be also used for maintenance of normothermia in the following days or hours. Moreover, in line with current indications to consider TH in pediatric victims of CA, several commercially devices have expanded their capabilities to manage temperature in patients of different sizes ranging from neonates to adolescents.

The maintenance of normothermia should not be underestimated as fever after all acute neurological insults is detrimental (including CA). However, it is not known until when it should be considered a hazard. Hence rigid normothermia for at least 3 days, particularly in those patients not regaining consciousness after rewarming and sedation hold [4].

A large amount of patients tend to become febrile after gradual rewarming and restoration of normothermia. In our first 4 years' experience we identified this as frequently occurring condition that could be ameliorable. Indeed in the first 32 months, we observed a hyperthermic rebound (defined as core temperature ≥37.8 °C) in the initial 12 h in 36 % of patients ($n = 21/58$); this rate increased up to 57 % ($n = 32/55$) when considering a longer period (48 h since restoration of normothermia). Accordingly, we modified our SOPs to include systematic antipyretic prophylaxis with paracetamol and if necessary reinstitution of deep sedation along with active temperature management. In the 16 months that ensued, hyperthermic rebound was significantly reduced to 3 % in the first 12 h ($n = 1/31$; $p < 0.01$), and to 29 % ($n = 7/24$; $p < 0.05$) when considering rebound up to the 48 h.

17.4 Monitoring and Post-Resuscitation Care

Accurate monitoring of core temperature is essential for target temperature management. Tympanic and rectal temperature should not be measured as they are unreliable and do not sensibly reflect rapid variations in the core temperature [16]. Esophageal temperature is regarded as the more reliable, followed by bladder. The goal standard remains central blood temperature which can be obtained from pulmonary artery catheter or femoral artery (i.e., PiCCO®) catheters. By all means, temperature should be continuously monitored. Some commercially available devices continuously acquire information from two temperature probes in order maximize patient safety [17].

Neuro-protective measures to mitigate anoxic brain injury include but are not limited to TH. Intubation and mechanical ventilation should be promptly instituted and monitored. Protective ventilation strategies should be pursued. Continuous end tidal CO_2 ($EtCO_2$) monitoring is essential to ensure normocapnia while modifying metabolic rate by inducing hypothermia and thereby CO_2 production. Ventilator settings should therefore be adjusted accordingly since CO_2 reactivity is maintained both in normothermic and hypothermic comatose CA patients [18, 19]. To the contrary auto-regulation of cerebral blood flow is often compromised [20, 21]. Hence, hyperventilation is associated with a reduction in mean blood flow velocities of the middle cerebral artery on transcranial Doppler assessment and with a reduction in jugular bulb venous saturation [18, 19]. Reductions in jugular bulb venous saturation in turn are accompanied by an increase in O_2 extraction, suggesting cerebral ischemia. Yet, normocapnia is not always maintained as reported by a Finnish study on 122 patients with over 1,600 blood gas samples scrutinized [22]. Patients were normocapnic for 54 % of the time, while for 12 % of the time $paCO_2$ was higher than 45 mmHg, and in 34 % it was moderately reduced (30–34 mmHg). Furthermore in 9 % $paCO_2$ was severely reduced (<30 mmHg).

Blood gas analysis can be run at 37 °C regardless of patient temperature (alpha-stat) or can be corrected for actual blood temperature (pH–stat method). When correcting for blood temperature in a hypothermic patient, pH value is higher, while $paCO_2$ and paO_2 are lower than when analyzing by alpha-stat. The issue is far from trivial as the pH–stat method prevents an inadvertent relative alkalosis of cerebrospinal fluid which increases neuronal excitability, thereby exacerbating excitotoxicity, and induces vasoconstriction which leads to decreased cerebral blood flow [23]. Animal models of focal brain ischemia undergoing hypothermia confirm a global reduction in cerebral blood flow, and either in blood flow to the ischemic or to the non-ischemic hemisphere, when ventilation is adjusted according to alpha-stat method [24]. Furthermore, volume of infarction was also significantly increased. Thus blood gas should be adjusted to patient temperature.

It is widely accepted that hypoxia aggravates brain injury. Yet, hyperoxia can also exacerbate secondary brain damage. Based on animal studies strongly supportive on increased injury following exposure to hyperoxia after ROSC, and a large clinical registry also suggesting a beneficial effect when avoiding hyperoxia ($paO_2 < 300$ mmHg), current guidelines recommend to titrate oxygenation as soon as possible to a target SpO2 of 94–98 % [7]. In this registry of 6,326 patients, 1,156 had hyperoxia (18 %), 3,999 had hypoxia (63 %), and 1,171 had normoxia (19 %) [25]. The hyperoxia group had significantly higher in-hospital mortality (63 %) compared to the normoxia group (45 %) and, interestingly, to the hypoxia group (57 %). When controlling for potential confounders (i.e., age, pre-admission functional status, comorbidities, vital signs, and other physiological indices), hyperoxia exposure had an odds ratio for death of 1.8 (95 % CI, 1.5–2.2). Although the issue is far from settled, while awaiting more sound evidence, there appears no reason to expose resuscitated patients to unnecessarily high oxygenation.

Post-resuscitation myocardial dysfunction is another well-known key element of the PCAS [26]. Myocardial dysfunction can manifest as a global myocardial stunning or as recurrent life-threatening arrhythmia. Management and monitoring depend on the degree of dysfunction but may require intensive support such as inotropic infusion (e.g., dobutamine or levosimendan) or mechanical support such as intra-aortic balloon pump or extracorporeal membrane oxygenation [16, 27]. Although reversible in the short period (from few days to a week), post-resuscitation myocardial dysfunction still remains the leading cause of death in first three days that follow resuscitation [26, 28].

The underlying cause of CA should be always sought. It is well recognized that post-CA patients with ST-segment elevation myocardial infarction should undergo early coronary angiography and PCI [7, 29]. It is worth reminding that chest pain and/or ST-elevation are poor predictors of acute coronary occlusion in these patients. Therefore, PCI should be considered in all post-CA patients who are suspected of having coronary artery disease [29] and should not be postponed because patients are unconscious. The combination of hypothermia and PCI is not only safe but recommended, as it appears to be associated with improved outcome [29].

Cardiovascular monitoring and particularly its endpoints during hypothermia are not ascertained. Hypothermia frequently induces bradycardia. A low heart rate is usually well tolerated and very seldom has been reported to require electrical or pharmacological pacing. To the contrary, recurrence of life-threatening arrhythmia appears to be reduced during hypothermia [12]. Adequate tissue perfusion can be indirectly derived from lactate clearance, urine output and normal SvO_2 levels. It is hard to recommend a specific mean arterial pressure range although it is imperative to avoid hypotension since loss of auto-regulation of cerebral blood flow should be always suspected. For this reason many centers currently aim at a mean arterial pressure of 65 mmHg or higher, for instance in case of previous history of hypertension [16].

A systemic inflammatory response is triggered by the ischemia and reperfusion that takes place during CA and resuscitation. This has also been identified as a ‘sepsis-like syndrome’, because the type and blood levels of cytokines closely resemble those found in septic patients [30]. Not surprisingly, these patients accommodate large quantities of fluids without increasing the rates of pulmonary edema or cardiogenic shock. Hemodynamic optimization and vasopressor support should not be withheld and may follow the early goal directed therapy principles [31].

Monitoring should also be directed at detecting and preventing the most adverse effects related to hypothermia. In particular the Hypothermia Network Registry reports, out of approximately 1,000 patients, pneumonia as a commonly occurring event (41 %), while bleeding requiring transfusion is low (4 %) despite it increases significantly in patients undergoing coronary angiography or PCI (2.8 % vs. 6.2 %) [9]. Sustained hyperglycemia (defined as blood glucose >144 mg/dl for >4 h) is also frequent (37 %), as are electrolytes disorders (hypokalemia, hypomagnesemia and hypophosphatemia, 18–19 %) [9]. The incidence of sepsis is low (4 %), but increases in patients with intravascular devices for temperature management (OR 2.6), IABP (OR 3.2) or undergoing coronary angiography (OR 4.4) [32].

Of note bleeding, infection, arrhythmia and electrolyte disorders were not associated with increased mortality. Only sustained hyperglycemia and seizures (despite treatment) were associated with worse outcome.

17.5 Neurological Complications and Multimodal Prognosis

Post-resuscitation brain injury is the leading cause of death after resuscitation. Epilepsy and myoclonus are a frequent neurological complication even in the era of hypothermia [4]. Before hypothermia was introduced in clinical practice, status epilepticus was one of the strongest predictors of poor neurological prognosis, and thus incompatible with meaningful survival. Yet, several reports demonstrate that previously accepted predictors of poor outcome in comatose survivors of CA are now unreliable if the patient has been treated with therapeutic hypothermia [33]. This has induced to actively monitor patients to promptly diagnose and treat epilepsy and myoclonus. At the same time a multimodal approach to prognostication has been proposed [4].

Clinical evaluation is unreliable but should be performed on a daily basis when possible in patients that remain unconscious [4]. For instance, EEG monitoring is highly informative: a continuous and reactive pattern is strongly suggestive of good recovery; a transition from continuous to status epilepticus is also compatible with good recovery, whereas transition from flat to epilepsy or status epilepticus without reactive background is associated with poor prognosis [34, 35]. EEG (Electroencephalogram) is a cornerstone to treat status epilepticus by inducing bust suppression through sedatives (i.e., propofol or benzodiazepines) while achieving the therapeutic range of antiepileptic drugs. Somatosensory evoked potentials are also extremely reliable in predicting poor outcome when cortical potentials (N20 waveforms) are bilaterally absent [4]. Finally, neuroimaging and biomarkers such as neuron-specific enolase can be used as aid in concurring to determine prognosis.

17.6 Conclusions

A structured approach to post-resuscitation care should address the key elements that constitute the post-cardiac arrest syndrome.Hypothermia as well as other treatments should be standardized is SOPs which should include specific instructions on monitoring. Monitoring is essential not only to ensure optimal intensive care but also to anticipate and detect possible adverse effects of hypothermia. Finally, patients that remain unconscious after restoration of normothermia require additional care and monitoring. Temperature management should continue for at least three days after ROSC and possibly longer; neurological complications should be sought and treated, and a structured multimodal prognosis endeavored.

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Part VIII
Humanization

Palliative Care in Pediatric Patients

18

Marinella Astuto, Giuliana Arena, Rita Scalisi and Carmelo Minardi

18.1 Introduction

When palliative medicine was recognized as a specialty in 1987, it was defined as "the study and management of patients with discomfort present, progressive and evolved, for whom the prognosis is limited and the treatment goal is quality of life" [1].

Each year in the United States, approximately 50,000 children die from and 500,000 children cope with life-threatening conditions. Worldwide these numbers are in the millions. Such children and their families require comprehensive, compassionate, and developmentally appropriate palliative care [2].

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18.2 Definitions

In 1990, the World Health Organization (WHO) stated that the control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care, in the WHO definition, is to achieve the best quality of life for patients and their relatives. Many aspects of palliative care are easily applicable in the course of the disease along with the antineoplastic treatment [3].

Palliative care for children is a developing area of care that is not yet widely recognized as a specialty in its own right. Palliative care aims to support children with life-limiting conditions and their families to maintain quality of life. It has been defined by the WHO as follows:

- Palliative care for children is the active total care of the child's body, mind, and spirit, and also involves giving support to the family.
- It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress.
- Effective palliative care requires a broad interdisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.
- It can be provided in tertiary care facilities, in community health centers and even in children's own homes.

Life-limiting illness is defined as a condition where premature death is usual, for example Duchenne muscular Dystrophy. A life-threatening illness is one where there is a high probability of premature death due to severe illness, but there is also a chance for long-term survival to adulthood; for example children receiving cancer treatment or admitted to intensive care after an acute injury. The term "terminal illness" is most frequently used to describe all children with life-limiting illness in addition to those with life-threatening illness when death becomes inevitable [4].

Four conditions are considered appropriate for Pediatric Palliative Care [2, 4–8]:

(1) Life-threatening conditions for which curative treatment may be feasible but can fail. Where access to palliative care services may be necessary when treatment fails. Children in long-term remission or following successful curative treatment are not included.
(Examples: Cancer, irreversible organ failures of heart, liver, and kidney.)

(2) Conditions where premature death is inevitable, where there may be long periods of intensive treatment aimed at prolonging life and allowing participation in normal activities.
(Example: Cystic fibrosis.)

(3) Progressive conditions without curative treatment options, where treatment is exclusively palliative and may commonly extend over many years.
(Examples: Batten disease, mucopolysaccharidoses, muscular dystrophy.)

(4) Irreversible but non-progressive conditions causing severe disability leading to susceptibility, to health complications and likelihood of premature death.

(Examples: Severe cerebral palsy, multiple disabilities such as following brain or spinal cord injury.)

The International Children's Palliative Care Network (ICPCN) is the only international network of organizations and individuals working within all children's palliative care services around the world.

18.3 Differences Between Palliative Care in Adults and Children

Children's palliative care differs from adult palliative care as follows [7]:

- The number of children dying is small.
- The conditions are extremely rare with diagnoses specific to childhood.
- Predicting a prognosis can be difficult.
- The palliative phase is often much longer and can be episodic and unpredictable.
- Children may experience several apparently terminal phases.
- Care embraces the whole family and uses a model of family centered care.
- Parents require adequate resources to support them with the heavy responsibility for personal and nursing care.
- Siblings are vulnerable and parents must continue to provide care for them while often providing 24 h care to a sick child.
- Conditions are sometimes familial—other children in the family may be living with, or have died from, the same condition.
- Children's ability to communicate and understand varies according to their age or stage of development.
- The provision of education and play when a child is sick is essential.

18.4 Pediatric Palliative Care: Looking at the World

Provision of pediatric palliative care around the world is scant. There are, of course, many reasons for this such as financial, lack of trained professionals, and a lack of general awareness by the public or policymakers. Despite these barriers, and many others, many countries have found ways to provide this care and these countries are both resource-rich and resource-poor. It is important for these countries to share their experience, which includes valuable information on how barriers were overcome and programs were developed and implemented. Only through information dissemination will countries with no programs be able to learn from others and to identify strategies that they can be used to help advance the pediatric palliative care movement worldwide [9].

In 2006, the European Association for Palliative Care (EAPC) formed the group called International Meeting for Palliative Care in Children, Trento (IMPaCCT) which was sponsored by the Maruzza Lefebvre d'Ovidio Foundation (Rome),

Fondazione Livia Benini (Florence), and the No Pain for Children Association (Trento). In 2007 the IMPaCCT group became an EAPC task force. Over 3 days, pediatric palliative care services in different countries were compared, pediatric palliative care was defined, best practices identified, and minimum standards agreed on. The result is a united document for Europe, defining and identifying standards of care for children with life-limiting and terminal illnesses. IMPaCCT recommends that these standards be implemented in all European countries [4].

In 2009, the National Hospice and Palliative Care Organization (NHPCO) published The "NHPCO's Standards for Pediatric Palliative and Hospice Care Advancing Care for America's Children" in order to improve methods and to create and sustain high-quality programming of pediatric palliative care [10].

In 2009, the Department of Health of Western Australia published a document entitled "Paediatric and Adolescent Palliative Model of Care". The Model of Care proposes all children and adolescents with a life-limiting illness, and their families, will have timely access to specialist palliative care services and expertise. The Model demonstrates the need for specialist pediatric and adolescent palliative care services in WA that meet the standards of a Level 3 Palliative Care Australia (PCA) specialist palliative care service. Services will provide developmentally and culturally appropriate palliative care regardless of the underlying diagnosis, geographical location, and chosen setting for care. The specialist pediatric and adolescent palliative care service aims to improve the capability of other health care services (primary, secondary, and tertiary) and supportive care organizations to provide comprehensive care to children and adolescents with life-limiting illnesses and their families [8].

In 2005, The International Children's Palliative Care Network (ICPCN) was founded. It is a worldwide network of individuals and agencies working with children and young people with life-limiting conditions. ICPCN shares a vision that the total needs of life-limited children and their families should be met, to encompass physical, emotional, social, spiritual, and developmental aspects of care. One of their key tasks is developing an "International Directory" of children's palliative care professionals across the world [11].

18.5 Pediatric Palliative Care in Italy

In Italy about 11,000 children (from 7,500 to 15,000) with an incurable disease and/or terminal (1/3 Cancer-2/3 noncancer), need pediatric palliative care.

In 2006, the Italian Ministry of Health produced a white paper entitled "palliative care directed to infants, children and adolescents" [5]. This document identifies the four categories of pediatric patients for whom palliative care is indicated. Assistance to pediatric patients who need palliative care is divided into three levels relative to increasing intensity of special needs and to increasing requirement of caregivers' skills. Common elements that characterize the child that cannot heal are: great variability of age, clinical conditions, and natural

history; relative rarity of clinical conditions requiring palliative care; high level of care needed; high complexity of the psychological picture surrounding a child's death. The growth of a child cannot be separated from his family, the child's, the family's, and caregiver's needs must be considered in palliative care. The expression "Profiles of intervention" well defines the overall care of the person, not running out in the mere delivery of a sum of individual performances, but the insertion of a "unified and predefined care plan". These actions may be organized according to the phases of multidimensional assessment and total care. Action on the child and on the family can be summarized as follows:

- Diagnostic assessment, involving general condition clinical assessment, clinical monitoring, evaluation of the physical environment, and social interaction, intrafamilial and of the family with wider community membership, communication, information.
- Taking charge in the palliative care network, which includes total medical treatments, psychosocial, educational and spiritual support, information, education and sensitization.

The intervention profiles are based on the presence and contextualization of four different modes of care delivery, two residential and two homes:

- Residential, for children hospitalized in acute care facilities, where palliative care is provided by specifically dedicated staff.
- Residential, for children in appropriate facilities called "Hospices", where palliative care is delivered.
- Home, for children cared for at home by a dedicated hospital/home team specifically trained in pediatric palliative care "Home Hospitalization".
- Home, for children cared for at home by a local team, "Integrated Home Care".

Evidence from different studies [12–14] has shown the following points:

- Families want their child to remain at home until his/her death;
- Children want to stay at home;
- The resources currently used for pediatric palliative care are inadequate;
- The availability of "pain relief" is inadequate;
- Accessibility to any pediatric palliative care services is often determined by where the child lives and the type of pathology (greater availability for cancer patients);
- Communication between the various professionals and institutions that care for a child with an incurable disease is poor and needs to be developed;
- There is an urgent need for training of professionals and volunteers involved in taking care of the child and his/her family.

Evidence derived from the studies reported suggests planning the organization of pediatric palliative care based on network models.

It is essential that pediatric palliative care is based on a well-defined individual care plan, proposed and accepted by the families, based on analysis: of the individual patient's needs, based on clinical diagnosis, the characteristics of the child and his/her functional capacity, of the individual psychological and socio

economic resources of the family. The economic- and social welfare existing in the territory where the child lives.

The planning of individual care plans is accomplished through the identification and collaboration of two well-defined professionals: the referral center case manager and the territorial case manager. The center case manager is the doctor who coordinates actions and takes care of the overall patient care. His tasks are to plan individualized care plans integrated with the territorial case manager, as well as with the family, making sure that they both have all the basic knowledge necessary to carry out correctly their tasks. The territorial case manager is, generally, the family pediatrician and has the role of managing the child's condition in his/her own environment. The territorial case manager must ensure an integrated territorial assistance by coordinating the work of existing facilities and services (area reference hospital, Social services district, school services, voluntary organizations, etc.).

In 2007, the Italian Health Ministry defined "Residential centers for children's palliative care" [15] as part of the national health network. These residential centers have to provide high-level assistance but have the characteristics of a "Children's House" where children's relationships and the family environment are respected and where privacy, social interaction, and development promotion are allowed. A structure for every 2–2.5 million people is necessary to ensure a good service. The ideal size is ten beds and dedicated spaces must be provided for babies-infants, children, and teenagers.

The staff consists of a multiprofessional team, experts in palliative care for children.

The services provided are:

- Symptom control, control and prevention of complications and co-morbidities;
- Maintenance of the physical, mental, emotional, social, and spiritual perspective of the Child's Quality of life;
- Support for the stages of the child personality development putting in place all measures to promote social-environmental interactions;
- Support for the child's growth, education, culture, creativity, and spirituality;
- Support for the family to understand and live with a child with special needs;
- Counseling activities;
- Organization of facilitated routes to home care;
- Meeting, information, and training of families;
- Management of mourning;
- Support for local teams.

In the same year, 2007, the Permanent Conference for relations between State, Regions, and autonomous provinces of Trento and Bolzano established that [16]:

- Assistance to pediatric patients who need palliative care is divided into three levels relative to increasing intensity of special needs and to increasing requirement of caregivers skills.
- The pediatric palliative care team must be properly trained and supported and has to ensure continuity of care.
- The care network must ensure a child with a life-limiting illness the response to current and future needs and family needs.

- For pediatric patients home care is the main objective to be achieved.
- Creation a pediatric palliative care networks must take place at the regional or superregional level.
- Regions choose the model to be implemented in relation to their specific characteristics.
- Regional technical group with representatives from the Ministry of Health should develop Guidelines and promote the palliative care network development in each region.

In 2008, a new white paper on pediatric palliative care [6] was produced to underline the inadequacy of the management system of pediatric palliative care although the topic had been defined by the "State-Regions" Conference in June 2007. The document emphasizes the limitations of the care model with four options: two residential and two home. Based on international experience, this document proposes the organization of a Reference Center of Excellence and a network of pediatric palliative care organized into macro-areas. Similar models exist in the United States and Australia where the health system provides a network of hospices integrated and related to satellite home assistance. The Reference Center for pediatric palliative care, with dedicated staff, should have a large catchment area (regional or supra-regional) and support a network composed of pediatric palliative care services in hospitals, local health departments, health and social welfare officer.

Law number 38, of March 15, 2010, aims to protect the right of citizens to access palliative care and pain therapy [17]. Under the essential levels of assistance, health facilities that deliver palliative care and pain therapy provide a program of individual care for the patient and his/her family, while respecting the following fundamental principles:

(a) protection of the dignity and autonomy of the patient, without discrimination;
(b) protection and promotion of quality of life up to death;
(c) appropriate medical support and welfare of sick persons and their families.

Italian Law agreed with the WHO definition of Palliative Care and defined, in the second article of Law 38, the concepts of: palliative care, pain therapy, patients affected by life-limiting/life-shortening conditions, national network for palliative care and national network for pain therapy, hospices, home care, day hospices, and pain management specialist assistance. In reference to pediatric palliative care, law no. 38 mentions: The Permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano, meeting on June 27, 2007, and the Ministerial Document on pediatric palliative care approved on March 20, 2008 in the Permanent Conference for relations between the State, Regions and autonomous provinces of Trento and Bolzano.

The professionals listed as leading figures of palliative care and the pain therapy network are: general practitioners and medical specialists in anesthesia and intensive care, geriatrics, neurology, oncology, radiotherapy, pediatrics, the physicians should have at least 3 years of experience in the field of palliative care and pain management, nursing, psychology, and social work as well as other professional fields deemed essential.

Article number 8 of this law specifies the role of the Minister of Education, University and research in planning a training plan for those involved in the management of palliative care.

18.6 Pediatric Palliative Care in the Intensive Care Unit

The PICU is the place where many children with life-limiting conditions die. What is missing in many clinical PICU settings is the range of personnel required to meet the many and varied needs of the dying child and his/her family. If palliative care for children is "…the active total care of the child's body, mind and spirit and also involves giving support to the family", it requires the participation of a dedicated team that may include disciplines such as social workers, pastoral services, child life therapy, and psychology, in addition to those of a physician and nurse skilled in end of life care of children. Pain and symptom management, communication with children and families, decision making, and setting goals together with a correct approach to the time of death are critical points in PICU pediatric palliative care management [18].

A correct approach to child's pain involves the use of validated methods such as the pain scale, to assess pain intensity and a good collaboration with the child's family in order to interpret all the child's expressions of pain because parents have unique insights into their own children [19].

Many children in the ICU receive a continuous infusion of sedatives and analgesics and some of them are placed on continuous infusion of neuromuscular blockers. Interrupt the use of neuromuscular blockers in order to assess the level of comfort and sedation [20] or carefully reduce the degree of sedation to better evaluate the level of consciousness and amount of pain is desirable in some circumstances. Non-pharmacological pain management techniques such as massage therapy and music therapy can be adapted for use in the ICU. Moreover, encourage parents to hold their critically ill child in their arms whilst the child remains connected to a ventilator and infusion pumps, is a way to humanize the course of the child in the ICU.

Children's age or illness or life-support technology can limit their ability to communicate their fears, wishes, dreams, hopes, and desires so an active collaboration between caregivers, families, and psychologists could be crucial to ensure a good communication with children. Besides the presence of personnel trained to support the mind and soul of both the child and their families, the presence of a series of physical facilities influence the quality of the families well-being and ability to cope with the traumatic experience of their child's death. Family rooms for overnight accommodation and kitchenettes, together with an open visiting policy, help to make the point that the parents are not "visitors" but are rather the key people with the most at stake in their child's illness. To support families' adaptation to the ICU environment, other useful resources can be written material

that explains the structure, hierarchy, and options available to them and the access to books, videos and web sites that are relevant to their own situation [18].

Decision making is a critical point in pediatric palliative care. One challenge of a pediatric palliative care team is to help parents to make decisions that respect the best interests of their child versus those decisions that may help to alleviate only their own legitimate suffering. It can be helpful for caregivers to ask parents to try to interpret what their child may be "telling" them in actions as opposed to words [18].

Setting goals can go from increasing the comfort and quality of life of the child, treating all the discomforting symptoms, to ensuring a peaceful death.

Planning for how death will occur, if possible, is another of the palliative care team's jobs. Knowing what the family's desires and expectations are at that moment is fundamental to alleviate their suffering. The family may appreciate being transferred to a private room, for some families it is important that the extended family get to say goodbye and to hold the child in their harms before extubation. Some families are keen for the child to go home or to a hospice on ventilator support with removal of the ventilator occurring once the child is at home or in the hospice [21].

After the death the family should be allowed to stay with their child in the room until they are ready to leave. Some parents appreciate being offered the opportunity to clean and bath their child's body with the staff. A discussion should take place concerning the possible benefits of an autopsy, in some situations an autopsy is compulsory. Families are usually appreciative of staff being present at the child's funeral, this is an opportunity for staff who were unable to say goodbye to the family after the child's death to do so now [22].

18.7 Conclusions

For the children involved and their relatives, palliative care represents an indispensable goal so that pediatric medicine does not stop at establishing that a treatment has failed or that a condition is incurable. but must go on to recommend the best way for the child to live with disease for this reason in the last 10 years a range of palliative care clinical programs has been developed in hospitals, hospices, home care programs, and long-term care facilities to help fill the gap between traditional hospital care and community-based hospice care.

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End of Life Care

19

Cristina Santonocito

19.1 Introduction

A do-not-resuscitate (DNR) order is a written medical option that documents a patient's wishes regarding resuscitation and, more specifically, his/her desire to avoid an overtreatment. The DNR order is one of the most important patient care directives that can be issued seeing that it has dramatic and irreversible consequences [1]. ADs are similar and equally important, but include withholding or withdrawing interventions. Resuscitation has the ability to reverse premature death but it can also prolong terminal illness, increase the family's anxiety, and have serious economical consequences [2]. Despite the desire to respect the patient's autonomy, there are many reasons why withholding resuscitation maneuvers may complicate the management of critical illness and perioperative care. Concerns regarding these care directives have been raised by health care workers, patients, and their families. Hence, this explains the need to seriously consider the issues surrounding DNR orders and ADs. The definition of DNR order doesn't change among countries, it is the attitude to deal with it that changes among countries. The objectives of this review will be to describe the different attitudes in various countries regarding these arguments and to present our contribution which focuses on a correct introduction of these issues to future health care provider generations.

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19.2 Epidemiology

Disparities have been ascertained worldwide and also in the United States. DNR orders are, often, stated to the seriously ill but seem to be underused—even among the sickest. More often than not, the diagnosis at admission and the functional impairment are less considered than the age of the patient. DNR orders are frequently stated to older patients, women, and patients with dementia. Furthermore, care directives are stated less often to Afro Americans, patients with Medicaid insurance, as well as those admitted to rural hospitals. DNR orders are significantly higher in private nonprofit hospitals, and also in smaller ones. On the contrary, they are lower in academic hospitals. Standardized rates of the use of DNR orders vary across the states and the highest rates are among patients from rural areas [3, 4]. However, few studies have investigated the role of hospital factors and in particular geographic variations with respects to the use of DNR orders [5].

19.3 Medical Futility, Informed Consent and Informed Assent

The definition and value of the "futility" principle in medical decision making has been extensively discussed and futility is currently being used in clinical practices across the United States and around the world [6]. The new definitions of "medical futility" were developed by a consensus statement of the Society of Critical Care Medicine's Ethics Committee and can be summarized in Table 19.1 [7, 8]. There is evidence that the process of obtaining "informed consent" may cause considerable distress for patients and families [9–11]. Curtis and Burt [9] contend that to get an "informed assent"—when the patient or family is explicitly invited to defer to the clinicians' judgment in favor of with holding or withdrawing life-sustaining therapy—is an appropriate, ethical alternative. It is understood that this alternative should not be offered when clinicians are uncertain about the possibility of success or when the clinicians' convictions about withholding or withdrawing treatment are based on their value judgments regarding the patient's outcome and quality of life. The ethical property of the assenting process depends on the clinicians' careful attention to the particular wishes and needs of specific patients and their families. It is equally true that the process of informed consent demands from

Table 19.1 Definitions of "medical futility"

Old definition	Reformulate today
✔ Nonbeneficial	Intervention that is unlikely to:
	✔ Restore
✔ Ineffective	✔ Maintain
✔ Inappropriate	✔ Enhance a life that the patient can be aware of

physicians that they have good communicative skills and that they spend more quality time with patients and their families [9]. An alternative to this is a written "comfort measures only" order. Nevertheless, even if expressed, it is insufficient for redirecting changes in the care of a dying patient. A DNR order is part of advanced directives and many other medical interventions may be withheld upon discussion with the patient or the patient's surrogate. The rationale of a DNR order is not to limit aspects of care, but to avoid overtreatment, and it should not be assumed as a limit for escalation of treatment, i.e. Intensive Care Units (ICU) admission.

19.4 Ethics and Advanced Directives

Around the world, there is still confusion about the meaning of advanced directives and how they have to be followed—the United States, European and Australian health care systems are still working out the details [12]. For a better understanding of the role of various forms of advanced directives, especially DNR order, it is important to consider that the motivating moral idea behind advance directives is similar to that of informed consent. Advance directives are, in essence, a proactive informed refusal of therapies in a future state of incapacity. Informed consent is typically used in the process of obtaining permission to perform interventions (e.g. placing a central line or going through a surgical procedure). Moreover, one of the moral bases for informed consent is to respect the patients' autonomous wishes. This is also true for ADs with respects to the four cardinal ethical points in Table 19.2. In the United States, apart from the living will, there is another autonomous statement of self-determination called the Durable Power of Attorney for Health Care (DPAHC). This statement requires the appointment of a surrogate by the patient according to his/her best understanding of the patient's wishes prior to the onset of his/her incapacity. It is the patient's informed request that determines what is actually best for him/her and can differ from person to person depending on his/her set of values. Without the patient's understanding of where his/her interest lies, a physician cannot know how to provide benefit or avoid harm to him/her. In the absence of an AD or proxy decision-maker, the general preference is to preserve life when possible. European authorities, on the contrary, after decades of debate favouring paternalism, have

Table 19.2 To solve every clinical dilemma: the four cardinal ethical points

Autonomy	The right of the patient to accept or refuse any treatment
Not maleficency	Doing no harm or, even more appropriate, no further harm
Beneficial	Implies that healthcare providers must provide benefits in the best interest of the individual patient while balancing benefit and risks
Justice	Implies the concern and duty to distribute limited health resources equally within a society, and the decision of who gets what treatment (fairness and equality)

Table 19.3 EU Institutions referring values and operating principles

Values	Principles
✔ Universality	✔ Quality
✔ Access to good quality care	✔ Safety
✔ Equity	✔ Care based on ethics
✔ Solidarity	✔ Patient involvement
	✔ Privacy
	✔ Confidentiality

now fully endorsed the ethical principle of autonomy [12]. Still, even though the legitimacy of surrogates is now recognized by physicians, new legislations emphasize the patients' autonomy all over Europe. These conclusions were evidenced by the values and operating principles recognized by the Council of the European Union in Table 19.3. In Australia, patients are allowed to plan in advance the medical treatments in the event of incapacity through the use of ADs. Such a policy is verified in jurisdictions where the statute ADs qualifying or actioning scope are prescriptive enough for organisations to expect all health professionals to appropriately observe them. Differences in ADs frameworks across Australian states and territories are still unclear and therefore, health professionals are in need of a policy to determine their expected response. ADs are frequently discussed and considered during stressful and urgent circumstances in Emergency Rooms (ER) and in (ICU). It is well-known that in emergency situations it is always difficult to verify the presence of a DNR order, and subsequently to make a quick decision while taking into consideration the family's presence on the scene [13]. For this reason, discussions about DNR orders and ADs should be essential part of the standard for continuing well-patient care even for all competent patients. The patient/physician dialogue ought to continue even after patients have filled-out any forms, allowing the patient to develop an overall view regarding future medical care and give them the possibility to change their minds over time.

19.5 Patients' and Physicians' Attitudes Towards the Discussion of DNR Orders

In the United States, physicians' attitude to discuss this issue is on the rise. An open dialogue should take place between each patient and nurse or physician, not only when the patient is in proximity of death but even before. This dialogue aims to express the values that could help guide a decision-making process when the patient is unable to make his/her own decisions. In addition to this, a patient can choose a family covenant- an open health care agreement that can facilitate advance care planning. The family covenant provides a framework for the patient,

his/her family, and the physician in an interactive dialogue. Since individual values are the relevant features of an AD, making those values clear and explicit can greatly assist the family and the physicians to achieve the patient's benefit. It is also necessary to identify how nurses and physicians perceive end-of-life care so that their communication can be improved [14]. Even today, physicians are more likely to discuss DNR orders only when the patient's prognosis is poor. It has been noted that despite the short surviving time of cancer patients, many have never signed an AD. This may be an indicator of suboptimal doctor/patient communication [15]. A full consensus still hasn't been given with regards to DNR order terminology. For instance, some authors argue that the term "do not resuscitate" (DNR) is ambiguous and should be replaced by "allow natural death" (AND) [16].

19.6 Legal Aspects of the DNR Order

In the past, legal precedents and ethical interpretations dictated that patients were expected to receive full resuscitation unless there was explicit documentation expressing the contrary [17]. The decision "not to resuscitate" was first legalized after the mid-1970s. In the USA the American Medical Association first recommended that decisions to forego resuscitation be formally documented. Furthermore, it was emphasized that Cardiopulmonary resuscitation (CPR) was intended for the prevention of a sudden, unexpected death—not the treatment of a terminal, irreversible illness [17]. Explicit DNR policies soon followed, and the patients' right to self-determination was promoted. The event that prompted the enactment of the Patient Self-Determination Act was the Cruzan case which involved a young woman who was left in a persistent vegetative state after being resuscitated from a cardiac arrest following a car accident. Her parents and husband went to Court against the state of Missouri to demand the removal of her life-support system. The case ended up in the Supreme Court who sided with the State of Missouri agreeing that the State had the right to require "clear and convincing evidence" that Nancy Cruzan would have wanted life-support terminated. Nevertheless, the Supreme Court upheld the legal standard that competent persons are able to exercise the right to refuse medical treatment. Only after the family found such "clear and convincing evidence", was Nancy Cruzan removed from life-support almost 12 years after her persistent vegetative state. Until the Cruzan case (1990), there had never been any law about the clarity DNR orders and ADs. After this precedent, the Patient Self-Determination Act (PSDA) went into effect in 1990, making ADs legally acceptable by statute in all 50 states. During the Cruzan case, the Justice emphasized the importance of clear oral and written instructions prior to incapacity, as well as a clear appointment of durable powers of attorney, as the means for an incompetent individual to exercise his/her choice. The PSDA of 1990 is now responsible for the reduction of the number of patents without written ADs [18]. The DNR issue was considered not only in out-patient clinics but in perioperative time too. After the 1990s, decisions were typically left to the attending

surgeon and/or anesthesiologist, and DNR orders were routinely suspended during the intraoperative and immediate postoperative periods. In 1991, several articles criticized this widespread practice [19]. In effect, concerns were raised that patients were forced to compromise their autonomy and right to self-determination in order to qualify for surgery. This led to a policy of 'required reconsideration'. The American Society of Anesthesiologists formalized this policy in a set of guidelines approved in 1993 and updated in 1998 [20].

19.7 Advances in Future Perspectives

There is evidence of several different DNR order polices throughout the world (Table 19.4) and the lack of a universal DNR order policy. In all countries, need of standardization appears clear and below are several contributions support the target for achieving a consensus in this critical issue [21].

19.7.1 Increase Communication

A good open dialogue is essential between patients, families, religious representatives, and hospital staff in order to clarify the patient's preferences if he/she is still mentally competent. A formal education directed towards physicians is urgently needed to improve the frequency, quality, and timing of discussions concerning DNR orders and ADs in undergraduate and postgraduate curricula in medical and nursing schools.

19.7.2 Code Status Discussions

The DNR order is the only order that requires patient consent to prevent a medical procedure from being performed; therefore, informed code status discussions between physicians and patients are especially important. It is challenging to find specific strategies that can improve the quality of code status conversations and enhance end-of-life care planning, but there are no guidelines for code status as of yet.

19.7.3 Consensus on Law

Today, advanced directives are a debated issue all over the world. In the future, it will be necessary to achieve a consensus on law. The challenge is to find common traits in the different beliefs and religions to gain a standard policy.

Table 19.4 DNR order around the world

Country	Policy
USA	Signed consent policy Witnessed verbal consent policy
South America	Oral orders take preference ADs: physician thinks to share with the patient in decision making
UK	An advance refusal has legal force
Spain	DNR decisions are clearly indicated to limit the therapeutic effort
France	Directives by the patient's family or a surrogate decision maker have only a consultative role Care decisions are made after a collegial procedure
Belgium	Law regulating euthanasia End of life decisions often occur within the context of multidisciplinary care
Norway	Withholding and/or withdrawing life-sustaining treatment were taken in the aftermath of a DNR order
Netherlands	Euthanasia and self-written ADs are legally binding
Italy	Guidelines (SIAARTI) but there is not a law The doctors decide what to do trying to respect and giving a right interpretation of patient's will
Israel	No consensual practice Strong ethnic and religious beliefs (e.g. Jewish religion considers the dying event as an uninterrupted, peaceful transition from life to death)
China	It is preferable that dying people exhale their last breath at home More DNR orders being written
Japan	The physicians could institute DNR order without consulting the family when the physician feels that a CPR is unjustified and futile (The Japan Society for Dying with Dignity)
Australia and New Zeeland	Most of patients prefer DNR orders to 'good palliative care' orders and prefer written orders

19.7.4 Increase Trust Among Patients, Physicians and Health Care Systems

Physicians should educate terminally ill patients with regards to their wishes concerning life sustaining treatment and provide psychosocial support so that patients feel comfortable about expressing their preferences. Avoiding futile interventions [6] (Table 19.1) would be an important step to increase trust between patients and healthcare systems.

19.7.5 Improve Standards and Quality of Care

In authorizing a DNR order, surrogates must face a strong emotional experience. Signing a DNR order is a process and not an isolated act. Good quality communication and psychological support from health care staff are very important. Prior discussions, documents such as living wills, and consensus among family members make it easier to determine the patient's wishes and carry them out when signing the DNR order.

Moreover, there is evidence that ADs (living wills) are associated with end-of-life expenditures and treatments. This results in significantly lower levels of Medicare spending [22]. To improve standards of care, it is important to consider the current guidelines for example, the AHA guidelines state that: "Out-of-hospital DNAR protocols must be clearly written and easily implemented for all persons involved (members of the healthcare team, patients, family members, and loved ones). DNAR documentation can take many forms (e.g., written bedside orders, wallet identification cards, identification bracelets, or predefined paper documents approved by the local emergency medical services [EMS] authority). The ideal out-of-hospital DNAR documentation is portable and can be carried on the person" [23]; even the ERC guidelines are useful for the orientation of healthcare providers [24]. However, what is stated in the guidelines is "suggested" and the way to carry it out depends on the different cultures and beliefs.

19.7.6 To Respect the Patient's Will and the Family's Role

The DNR order reflects the patient's desire after full cardiopulmonary arrest. Correct interpretation of living wills and DNR orders is essential if patient safety and autonomy are to be preserved. The living will is an expression of informed consent or refusal before the patient becomes terminally ill (or persistently vegetative) and/or has lost his/her decision-making capacity. The patient's benefit is at the ethical center of advance directives, and his/her wishes are crucial for understanding what is best for him/her. The family is often involved in the decision-making of the critically ill (Fig. 19.1). Family dynamics and medical/legal concerns most often affect decisions to obtain/write a DNR order for critically ill

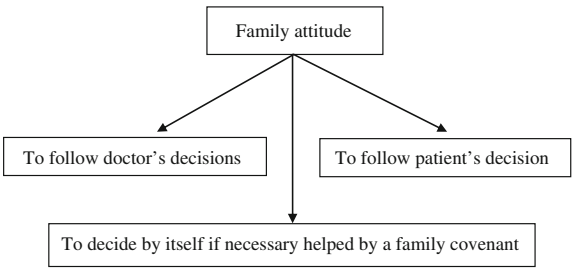

Fig. 19.1 Family attitude in case of end of life care

patients. Complicated situations may occur when family members do not support the goals of care determined by the patients. In this case a figure such as a family health-care provider or a family covenant can be helpful to mitigate conflicts.

19.7.7 Continue Education on Professionalism

Ethical values in clinical practice, especially patient autonomy, should be addressed during the early stage of the medical curriculum. The education, scholarship and ethical values of the Medical Professionalism proclaims concepts such as: maintenance of competence, ethical behaviour, integrity, honesty, relationship, responsibility, accountability, service to others, adherence to professional codes, justice, caring, compassion and altruism but also include respect for others and self regulation [24, 25]. This means that what should be taken into consideration is the patient's will and not what physicians think is "better".

19.8 Conclusion

After these considerations, it is clear that a serious professional reflection is absolutely necessary concerning end-of-life care. Despite the ardent desire to sustain life, medical professionals should withstand the temptation to act when the patient's wish is to not be resuscitated. Rather than perceiving that they are *doing nothing*, something has indeed *been done*: the patients' wishes have been respected, their autonomy has been preserved and they have been allowed to die with dignity. Unfortunately, complying with these wishes still represents a real challenge for patients and their families, physicians, nurses, as well as the society.

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