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Review

Evolution of medical ethics in resuscitation and end of life

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ABSTRACT

Medical ethics has evolved from paternalistic to patient-centred. Emergency and end-of-life situations are frequently associated with inability to make informed decisions. Respect for advance directives, proxy informed consent for therapeutic/research interventions, do-not-attempt resuscitation orders, and withdrawal of life-sustaining treatment focus on autonomy and nonmaleficence. Beneficence is increasingly interpreted in terms of “achieved quality of life” following emergency treatment/resuscitation. Justice pertains to equality of access to best available care, which depends on patient age, comorbidity, preferences, socioeconomic status, race, ethnicity, and religion. Dignity includes the concept of “dignified death;” the still-debated practice of physician-assisted death is gaining ground. Honesty/transparency augments patient participation in shared decision-making and treatment selection. A still-prominent, international variation in bioethical principles interpretation mandates continuous effort for harmonization.

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Contents

1. Introduction	00
2. Autonomy	00
3. Beneficence	00
4. Nonmaleficence	00
5. Justice	00
6. Dignity	00
7. Honesty	00
8. Unresolved problems	00
9. Conclusions	00
References	00

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1. Introduction

Founded through the Hippocratic Oath, medical ethics has evolved across the centuries using primarily virtue-centred, deontological, and paternalistic models to define ethical practice [1,2]. In 1847 the American Medical Association adopted the first code of professional ethics in medicine [3]. The basic concept of informed consent (IC) was first introduced in Prussian law in 1891

[4]. Immediately after the second World War, the Nuremberg Code was formulated [5]. The first of the ten principles begins as follows: “*The voluntary consent of the human subject is absolutely essential.*” The traditional principles of modern ethics (autonomy, beneficence, nonmaleficence and justice) were developed by Beauchamp and Childress in 1979 [6].

Increasingly, current ethical practices are underpinned by respect for patient preferences and autonomy, as opposed to traditional paternalistic approaches. This evolution is affected by extraordinary developments in resuscitation science and life-sustaining treatments, since emergency/end-of-life situations are frequently associated with compromised patient decisional capacity and IC validity [7]. To address these problems, a growing body of publications focuses on the extent and effects of the contemporary, autonomy-prioritizing application of the bioethical principles. This may underpin an era of “evidence-based” ethical practices. The current paper aims to review the recent evolution of ethical practices in the setting of emergency care and end-of-life situations.

2. Autonomy

The principle of autonomy (*αυτοξ-αυτος* = self and *νόμος*, *nomos* = rule), reflects the right of a person to make his/her own decisions, without external control [7]. The respect for the right of self-determination constitutes an essential part of current medical practice. Patient centricity has challenged medical paternalism [8–10]. Competent patients may participate in their own health care planning, accept or refuse medical treatment or procedures, and express their wishes in an advance health care directive to be respected in case of future incapacitation. However, patients may not receive all treatment they request [10].

Following introduction of cardiopulmonary resuscitation (CPR) in 1960, the application of the autonomy principle became relevant for emergency care. CPR outcomes are improving continuously [11,12]. However, many patients with end-stage diseases die in a hospital and cardiac arrest is the final common step in the dying process [13]. CPR may postpone an expected natural death, thus counteracting patient preferences [14].

Advance directives or living wills are documents containing preferences of individuals regarding procedures or interventions in the event they lose decisional capacity in the future. The durable power of attorney enables people to appoint (trusted) “healthcare proxies” (e.g. a relative or friend) to decide on treatment(s). Advance directives emphasize the right to consent to or decline any medically indicated treatment, including life-sustaining treatment [8].

The concept of Do Not Attempt Resuscitation (DNAR) was a topic of controversy for many years [15] and is now accepted as an expression of patient’s preference or physician’s judgment. Better education and information has encouraged patients to autonomously contribute to decisions on their health or dying process [16]. A decision is regarded as autonomous when the patient has decisional capacity and sufficient pertinent information, and discloses his/her decision voluntarily. The respect for autonomy requires creating the necessary conditions for an autonomous choice.

Standard medical treatment and clinical research are distinct activities [17]. Patient’s autonomy may affect the feasibility of emergency clinical research. Indeed, to include participants in a study, IC must be obtained. In emergencies, there is often insufficient time to obtain IC. Other consent models are ethically acceptable alternatives for respecting autonomy in emergency research, such as exception to informed consent with prior community consultation [7,18–20] prospective IC [20,21], integrated clinical IC [20] consent from professional legal representative

[20,22] and deferred IC [7,19–22] (Table 1).

A recent European Union (EU) Regulation permitting deferred consent is expected to harmonize and foster emergency research across Member States [7]. An exception to written informed consent has been recently proposed for comparative effectiveness research [32] this proposal is currently the subject of intense debate [33].

3. Beneficence

The concept of beneficence means that, following an assessment of relative risk and benefit, interventions are selected for their potential to benefit the patient [34]. CPR benefit is not questionable, because no resuscitation means irreversible death. Exceptions to this rule are patients in whom cardiac arrest represents the terminal event of an irreversible disease and in whom resuscitation is not desirable. In all other situations, CPR is the only way to restore spontaneous circulation and prolong survival.

Recent data showed that an increasing proportion of victims are now surviving to hospital admission and discharge [11,12,35]. Resuscitation may be judged as “successful” when the individual is not cognitively impaired and reports an “acceptable quality of life” [36] or they experience no significant deterioration relative to their pre-morbid state [34]. Historically, such assessment has been underpinned by a clinician’s report of outcome – often utilizing crude neurological assessments such as the Cerebral Performance Categories (CPC) or Glasgow Outcome Scale (GOS), with a limited assessment of the patient’s perspective [37]. Moreover, long-term assessments of outcome following hospital discharge are infrequently reported [37,38]. There is growing awareness of the limitations of such short-term, clinician-based assessments – in particular, the potential to underestimate disability and cognitive impairment [39,41], the discrepancies that exist between clinicians, patients and loved ones in defining a good outcome [37,39] and the importance of longer-term follow-up [36,40]. The importance of adequately assessing the survivors’ perspective over both the short and longer-term is now recognised in both the updated international Utstein statement for cardiac arrest registries [42] and the recent core outcome set guidance for cardiac arrest clinical trials [36].

4. Nonmaleficence

Nonmaleficence stems from the Hippocratic axiom “help or at least do no harm” (“*primum non nocere*”). This principle comprises avoidance of harm or inflicting the least harm possible to reach a beneficial outcome [43]. Nonmaleficence involves practices of resuscitation and end-of-life decisions and is interdependent with patient autonomy and dignity.

CPR should not be performed in futile cases [35,44]. Futile CPR offers no reasonable hope of good-quality survival. Contraindications to CPR include obvious signs of irreversible death or “recognition of life extinct” (e.g. rigor mortis, decapitation, or decomposition), presence of advance directives, and rescuer exposure to risk of serious injury/death [44]. Regarding hospitalized, severely ill patients, DNAR decisions do not always require consent from patients or their surrogates, who may have unrealistic expectations about the potential benefits of resuscitation, especially after the advent of new technologies such as extracorporeal CPR [44]. The provision of accurate and accessible information to support the active involvement of patients or their surrogates in the decision-making process is essential [10,45,46]. A recent multicenter study showed that surrogates’ interpretations of physicians’ debriefing statements conveying a high risk of death are often inaccurate due to “optimistic biases” [47].

Table 1
Characteristics of models of informed consent for emergency clinical research.

Consent model	Prerequisites	Advantages	Disadvantages
EFIC with Community Consultation	<p>Life-threatening condition [18]</p> <p>Current treatments are unsatisfactory or unproven [18]</p> <p>Need for new and valid evidence for treatments [18]</p> <p>Inability to obtain IC [18]</p> <p>Possibility of direct subject benefit from research participation [18]</p> <p>Inability to conduct the research without the waiver [18]</p> <p>Definition of therapeutic window for contacting an LR [18]</p> <p>Research Ethics Committee approval of IC procedures [18]</p> <p>Public disclosure and community consultation [18]</p>	<p>Fast recruitment of a great number of patients [20]</p> <p>Opt-out options may be feasible [23]</p>	<p>Respect for autonomy applied at community-level but not at patient-level</p> <p>Public disclosure and community consultation has been associated with very low (i.e. 5%) levels of trial awareness among actual participants [24]</p>
Prospective IC	<p>Adequate resources such as manpower and funding [20,21]</p> <p>Identification of “high-risk” group in the general population [20,21]</p>	<p>It respects the patients' autonomy principle [20,21]</p>	<p>Resource demanding: Assuming a 1% chance of the emergency condition's occurring in the “high-risk” group, 10,000 people have to be consented to enrol 100 in the clinical trial [20,21]</p> <p>Need for robust mechanism for differentiation of those who consented from those who refused or were not approached [20]</p> <p>Research candidates may unconsciously alter their behaviour to reduce risk, thus augmenting the uncertainty about the prospect of reaching an adequate sample size (Hawthorne effect) [20,21]</p> <p>The low chance of actually being in the trial may compromise IC validity due to possible lack of due consideration of pertinent risks and benefits [20]</p>
Integrated clinical IC	<p>Pragmatic trial comparing commonly used treatments.[25]</p> <p>Interventions have already been validated through high-quality, randomized clinical trials [25]</p> <p>In ordinary practice, treatments involve only verbal IC.[25]</p> <p>Adequate resources such as manpower and funding</p>	<p>It respects the patients' autonomy principle [21]</p> <p>It can include most of patients from the community with this emergency condition [21]</p> <p>Simplified IC procedure reducing research workload [25]</p>	<p>Need to contact as many members of a community as possible. Need for robust mechanism for differentiation of those who consented from those who refused or were not approached [20]</p> <p>It may not be feasible in regions with diverse and complex communities [21]</p>
Professional LR IC	<p>General training on the role and responsibilities of a professional LR, e.g. understanding of the concept of clinical equipoise [26]</p> <p>Specific training: Professional LR must be informed of the nature, objectives, significance, risks, inconveniences and implications of the trial, and the conditions under which it will be conducted, and the right to withdraw consent to a subject's participation at any time [26]</p> <p>Professional LR must be independent of the research project [26]</p>	<p>It respects the patients' autonomy principle, even in the absence of a personal LR [26]</p>	<p>Personal professional LR beliefs with respect to actual presence clinical equipoise and efficacy of compared treatments may affect the IC procedure [26,27]</p> <p>Professional LR may be unaware of patient's preferences</p> <p>Varying interpretations on the definition of professional LR [20,22]</p>
Deferred IC	<p>Life-threatening condition – inability to obtain IC from the patient [28]</p> <p>Potential for direct, research-related benefit to the subject, in terms of outcome, or alleviation of suffering, or improvement in the diagnosis of its condition [28]</p> <p>Inability to obtain a valid IC from the subject's LR [28]</p> <p>Investigator not aware of any previously expressed patient objections with respect to trial participation [28]</p> <p>The clinical trial relates directly to the subject's medical condition [28]</p> <p>The clinical trial may be conducted exclusively in emergency situations [28]</p> <p>The clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition [28]</p>	<p>It respects the patients' autonomy principle, and enables the conduct of much needed emergency research [7]</p> <p>Not excessively resource demanding.</p> <p>It ensures “balanced” application of the principles of bioethics [7]</p>	<p>Absence of legal definition of consent for procedures that have occurred previously [7,29]</p> <p>Potential discrepancies between patients and their surrogates regarding willingness to grant IC [30]</p> <p>Surrogate IC validity may be affected by their ability to comprehend the study protocol under conditions of psychological stress and uncertainty about the patient's outcome [31]</p>

EFIC, exception to informed consent; IC, informed consent; LR, legal representative.

Validated prognostication tools may provide robust criteria for advance care planning, including withholding or withdrawing of life-sustaining treatment (WLST) and DNAR orders [48]. For example, in critically ill adult patients resuscitated successfully from in-hospital cardiac arrest, a large registry-based prediction

model may enable identification of those with very low (i.e. <3%) probability to achieve neurologically favorable survival [48]. Prognostication is substantially more challenging in neonates, and especially in extremely preterm (i.e. <25 weeks gestation) neonates [44]. Variations in physician attitudes towards decision making that

may impact how decisions are communicated to families have been described [49]. Evidence supports a structured discussion with parents focusing on the baby's severity of illness, professional opinions and options, basic human interactions (politeness, tolerance of bereavement-associated behaviour), the parents (their stories, needs, concerns, and goals), provision of information tailored to parental needs, and parental ability to cope with the situation [50].

Regarding termination of resuscitation (TOR), a previously employed rule was challenged by unexpected, out-of-hospital cardiac arrest (OHCA) survival rates of 3–9% [44]. TOR should be considered in cases of asystole lasting for >20, min despite ongoing advanced life support, and in the absence of a reversible cause [34,44]. In neonates with an APGAR score of 0 after 10 min of resuscitation and undetectable heart rate, discontinuation of assisted ventilation may be considered after taking into account the availability of advanced care, the timing of the insult, and wishes expressed by the family [44,51–54].

Current American Heart Association Guidelines state that “DNAR and discontinuation of life-sustaining treatments are considered as ethically equivalent and clinicians should not hesitate to withdraw support when survival is highly unlikely” [44]. Should this also include artificial nutrition and hydration in cases of confirmed, persistent vegetative state (PVS) after successful resuscitation? The controversy surrounding this issue is effectively illustrated by the 15-year long legal struggle of the Terri Shiavo case, a PVS patient in whom artificial nutrition/hydration was discontinued based on court ruling with respect to patient's preferences [55].

5. Justice

Justice can be procedural or distributive [56]. Procedural justice means that all patients have equal rights to healthcare, with healthcare providers legally obliged to provide appropriate care [56]. Hence, receipt of emergency healthcare is a ‘basic’, procedural right. Distributive justice pertains to the fair allocation of burdens and benefits by decision makers [56], e.g. a physician's decision on how much time to spend with each patient [56].

In the emergency setting, justice pertains to the equality of access to best available resuscitation/emergency and post-resuscitation/intensive care. According to a survey of key opinion leaders from 31 European countries [57], access to best available care is frequently (>25% of the countries) affected by comorbidity, age, location/type of admitting/treating hospital, and knowledge of expressed patient wish about receiving CPR. Other factors include socioeconomic status, high-risk presentation, race, and religion [57]. Indicators of emergency care organization level also exhibited substantial variation. This variation was mainly explained by differences in healthcare infrastructure for emergency situations (e.g. availability of telephone CPR and ambulance response times), availability of defibrillation [including public access defibrillation (PAD) programs], level of care provided by ambulance personnel, in-hospital practice of CPR debriefing, feedback and audit, and registry reporting of cardiac arrest [57].

The evolving European migration crisis implies that race and religion may soon become stronger determinants of access to specialised care. The routine planning for critical care services' expansion has not foreseen migration-related, sudden changes in population size [58]. This may result either in restrictions in intensive care unit (ICU) admissions or increasing numbers of premature ICU discharges to accommodate new patients [58]. Demand-based, ICU admission and discharge policies should be defined [59]. Admission prioritization should depend on disease severity and expectation of recovery, rather than nationality, ethnicity, race, religion, or culture [58,60].

In the United States (US) and Taiwan, higher regional socioeconomic status is associated with a higher likelihood of bystander CPR [61,62], a key predictor of survival from OHCA [63]. In Japan, good-quality bystander CPR is more likely in the central/urban region [64]. In Denmark, residential locations have been associated with delayed ambulance responses, a lower incidence of shockable, first recorded rhythms, and worse 30-day OHCA survival compared to public locations [65]. In the US, there is regional variation in both OHCA [66] and in-hospital cardiac arrest (IHCA) outcomes [67]. OHCA outcomes variation is likely explained by regional differences in bystander CPR, PAD, rescuers' expertise and experience, and available treatments at receiving hospitals [66]. Several investigators [68–73] have suggested an association between patient socioeconomic status, race, ethnicity, nationality, and OHCA outcomes. A large US IHCA registry has shown that black patients have lower survival to discharge than white patients [12]. It is unclear whether this finding is mainly due to differences in quality of care and/or patient characteristics.

In summary, in the emergency setting all patients in a critical condition should be considered for optimal care, without taking into account their administrative situation.

6. Dignity

The concept of dignity is multidimensional. Basic or absolute dignity has been defined as the intrinsic moral worth of all people whereas personal dignity depends on subjective values of the individual, such as autonomy, meaningfulness, physical comfort, spirituality, and interpersonal connectedness [74]. From a patient perspective, dignity includes *illness-related concerns, preservation concerns and social concerns* [74,75].

In the context of resuscitation and end-of-life situations, the concept of dignity pertains mainly to the “right to a dignified death” [75–81]. Respect for this right may correspond to DNAR, advance directives, and WLST. In addition, the “right to die” can be realized through physician-assisted death (PHAD).

In the US Declaration of Independence, human rights include “Life, Liberty, and the pursuit of Happiness” [56]. The Canadian Constitution mentions the rights to “Life, Liberty, and Security of the Person.” In both countries, there are currently either regional or federal, legal frameworks supporting the option of PHAD as requested by decision-capable, terminally ill patients [75–78,81]. In Canada, PHAD is designated as “medical treatment” [75]. In South America, prescribing lethal medication administered by a clinician is allowed in Colombia [81]. In Europe, PHAD is a legal end-of-life option with a prerequisite of “unbearable suffering not necessarily coinciding with terminal illness” in the Netherlands, Belgium, Luxembourg, and Switzerland [76,79,80]. In many European countries, an intensive pro-con debate about PHAD is ongoing.

To our knowledge, there is no explicitly defined constitutional right to “Death” in any supporting, pertinent legislation [81]. Nevertheless, such right could be regarded as consistent with “Liberty, Autonomy, and Dignity” [76,77]. Physicians who cannot morally accept PHAD should present alternatives to the patient, including referral to another doctor [78,82]. PHAD can be applied as euthanasia or assisted suicide. Euthanasia (from Greek: *eu*, *eu*: “good”; *θάνατος*, *thanatos*: “death”) pertains to the intentional and painless termination of life by somebody other than the person concerned at his or her request. Euthanasia is legalized in the Netherlands, Belgium, Luxembourg, Canada, and Colombia [76,80]. Assisted suicide means intentionally helping a patient to terminate his or her life at his or her request. Physician assisted suicide is legalized in Canada, the Netherlands, Switzerland, and some USA states.

According to reports from the US and European countries about

incidence, demography, pathology and motives of PAHD patients, the variability of characteristics reflected the differences in legislation, attitudes, and practices [80,83–86].

In the pro-con debate about PAHD (ongoing in many countries), the following arguments are used against PHAD [87–90]:

- Patients already have the right to refuse life-sustaining treatment and receive palliation (e.g. opioids for pain control), even if this treatment has a “double effect” (i.e. analgesia, and potentially lethal respiratory depression).
- Patients also have the possibility to end their lives without involving physicians.
- The “right to die” may be considered a euphemism for the “right to have a physician help me kill myself.”
- The right to self-determination does not justify PHAD, and that caregiver trustworthiness may be of concern when the patient can no longer take care of himself or herself.
- PHAD contradicts the physician’s professional role; physicians are not merely service providers accommodating self-determining decisions of patients; the physician’s constitutive role is to help patients endure their suffering, and not terminate their lives.
- Finally, PHAD does not accord with the Hippocratic Oath.

7. Honesty

Increasingly, patients expect to participate in shared decision-making and exploring how different treatment options may fit with their own values and preferences. The medical professional supports this process by facilitating the exploration of patient preferences and the honest, transparent and accurate integration of such wishes with best research evidence and clinical judgement. For example, where treatment would confer no benefit. The provision of such considered information empowers patients to exercise their informed choice for care.

Inappropriate CPR may cause unnecessary distress and pain, resulting in an undignified death. However, members of the public may have unrealistic expectations about the benefit of CPR [44]. Awareness of the invasive nature of CPR, injuries associated with attempted CPR, poor survival rates post cardio-respiratory arrest, and the possibility of brain injury in cardiac arrest survivors is generally low [91].

Honesty requires clinicians to speak frankly about death and to communicate accurate, complete and un-biased information to patients, their loved ones and/or legal representatives about the relative benefit of CPR with which to support decision-making. Where patients have a “terminal illness” or are at the end of their life [92], the relative risk/benefit of CPR can be discussed and an advance directive instituted: such informed decisions require patients to know that they are nearing the end of life and what type of care will be available at each stage. However, the provision of such information must be combined with sensitivity and compassion: good communication skills are essential [92].

Effective, compassionate communication between clinicians, patients and family members is an essential component of patient-centred care, requiring an appreciation of both the medical and numerous non-medical challenges faced by patients and their loved ones at the end of life [34,91,93]. However, the time-limited nature of emergency situations challenges the ability to establish interpersonal relationships and effective information exchange – advance directives are often unavailable or unknown. Care and CPR decisions must therefore be made on the basis of individual assessment, and where an individual lacks capacity, a suitable proxy consulted. Treatment decisions are founded on the judicious

integration of research evidence, professional judgement about likely benefits or risks from treatment, and an awareness – where possible, of patient and family values and wishes. The accurate, complete and un-biased communication of such decision making to patients, family members and/or legal representatives supports the development of realistic goals and expectations from treatment [93].

8. Unresolved problems

Despite the progress in legal recognition and clinical use of advance directives and DNAR [57,94,95], end-of-life practices still vary substantially at an international/EU level [19,57,95]. This reflects legal, socio-cultural, mentality-related/philosophical, religious, and economic differences among variably developed countries [8,57]. There is evidence of significant variation in international progress from the paternalistic to the patient-centred ethical approach, thus mandating continuous efforts to maximize harmonization of pertinent legislations, and most importantly, of “every-day/routine” interpretation/application of the bioethical principles.

End-of-life practices and decisions are not devoid of problems:

- Living wills of healthy persons are frequently drafted in ambiguous terms to cover the broadest spectrum of possible, future disease states, and this may hinder their clinical applicability [8]. Advance directives can be misused by doctors or family members to neglect patients, may contradict attending physicians’ professional opinion, and constitute a highly individualistic decisional approach that disregards the role of the family [8].
- DNAR may reflect the patient’s preference or the physician’s judgment: do not start CPR in case of cardiac arrest. Pertinent implications may be variably interpreted and/or extrapolated to other aspects of care. Various “acronyms” have been proposed to specify end-of-life management. These include DNACPR - “do-not-attempt CPR”; POLST - “physicians orders for life-sustaining treatment”; WLST - “withdraw/withhold life-sustaining therapy”; AND - “allow natural death”; NFR - “not for resuscitation”; and UFTO - “universal form of treatment options.” Consensus to prevent caregivers’ confusion could improve quality of care.
- DNAR practice can also be problematic. Reported shortcomings include poor communication with patient/family, disagreement with DNAR decisions, failure to plan for DNAR, poor record keeping and handover of DNAR decisions between health-care settings, failure to implement DNAR, healthcare provider confusion over decision-making processes, and lack of DNAR reviewing according to changes in patient status [94]. DNAR decisions resulted in withholding of invasive treatments, reduced personnel vigilance, less basic care including pain relief, and altered fluid intake [94].
- As in the case of TOR (see above), decisions to withdraw/withhold life-sustaining therapy (WLST) should be based on robust/evidence-based criteria, as otherwise they may cause harm, especially if taken too early, e.g. within 72 h postresuscitation [96]. The European Resuscitation Council and European Society of Intensive Care Medicine have recently published cardiac arrest prognostication guidelines [97] that may promote nonmaleficence.
- Emergency research can also support nonmaleficence. Indeed, testing of traditional but still un-validated interventions, such as epinephrine during CPR [98,99] may prevent future exposure of many incapacitated patients to intervention-associated hazards). In the EU, a new Regulation is expected to harmonize and foster low-risk emergency research; however, regulatory

improvements are still needed for emergency surgical research and research on non-medicinal interventions [7,28].

- Published evidence suggests that at international level, access of cardiac arrest patients to the best available emergency care (as well as its quality) may vary according to both regional and patient-related factors. However, the principle of justice requires fair and equal opportunity in life for all persons. Consequently, there is still space for substantial improvement in the application of procedural and distributive justice, even in countries with high-level emergency care organization.
- Given the conflicts between autonomy and dignity of a competent adult who seeks death due to an “unbearable” and/or terminal disease, the sanctity of life and need to protect the vulnerable, the limited and variable application of PHAD [57,75–86] and the presence of influential opposing organizations [87], the final outcome of the currently emerging respect for the “right to die” may be quite uncertain.

9. Conclusions

End-of-life and resuscitation ethics has evolved to become an evidence-based, patient centred and balanced application of the Principles of Bioethics. However, substantial effort is still required to promote international harmonization of legislations and limit the diversity in the interpretation/application of these principles. Despite substantial progress with respect to autonomy and non-maleficence, there are still important unresolved problems concerning justice and controversies concerning dignity and the “right to die.”

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