Chapter

Determination of Death: Ethical and Biomedical Update with International Consensus

Md. Shah Alam Panna

Abstract

Humanity has been confronted with the concept and criteria of death for millennia and the line between life and death sustains to be debated. The profound change caused by life support technology and transplantation continues to challenge our notions of life and death. Despite scientific progress in the previous few decades, there remain big variations in diagnosis criteria applied in each country. Death is a process involving cessation of physiological function and determination of death is the final event in that process. Legally, a patient could be declared dead due to lack of brain function, and still may have a heartbeat when on a mechanical ventilator. Though there is no point in supporting ventilation in a dead person, withdrawing a ventilator before the legal criteria for death may involve the physician in both civil and criminal proceedings. To identify the moment of death is vital to avoid the use of unnecessary medical intervention on a patient who has already died and to ensure the organ donation process, clear and transparent. The age-old standard of determination of death is somatic standard and cardiopulmonary standard. Harvard report (1968) defines *irreversible coma* as a replacement criterion for death and prescribed clinical criteria for the permanently nonfunctioning brain. The current unifying concept of death: *irreversible loss of the capacity for consciousness combined with irreversible loss of the capacity to breathe*. WHO (2014) adopted minimum determinant death criteria, acceptable for medical practice globally, achieving international consensus on clinical criteria to maintain public trust and promote ethical practices that respect fundamental rights of individuals and minimize philosophical and biomedical debate in human death. AAN (2019) endorses that the brain death is the irreversible loss of all functions of the entire brain and equivalent to circulatory death.

Keywords: definition of death, determination of death, bioethical issues of death, death determinant, controversies on death declaration, death declaration, international consensus on death declaration

1. Introduction

> *"The term brain death signifies that there is more than one variety of death. This is a serious misconception, perpetuated by such statements as "the patient declared brain dead at 3:00 a.m. on Thursday and died two days later." There is only one real phenomenon of death that clinicians and families struggle to recognize."*

"A case of Elaine Esposito who lapsed into coma following surgery on August 6, 1941 and died on November 25, 1978, 37 years and 111 days later."

*President council (2008) of bioethics**

Death is often considered in terms of medical, legal, ethical, philosophical, societal, cultural, and religious rationales. The biomedical definition of death is primarily a scientific issue supported by the best available evidence. A medical practitioner has certain ethical and legal responsibilities regarding death, such as the effort for prevention of death, determination of death, determination of time/moment of death, declaration of death, issuing the certificate, and if needed, autopsy or organ removal for transplantation. That aspect has a lot of ethical, legal, emotional, and scientific issues. Dying is considered as a process, which affects different functions and cells of the body at different rates of decay. Doctors must decide at what moment along this process there is permanence and death can be appropriately declared. Diagnosis of death and a record of the time of the death, in most countries, are the legal responsibility of a medical practitioner. Determining the moment of death is vital to avoid the use of unnecessary medical interventions on patients who have already died and to make sure that the method of organ donation is obvious and transparent. Also, the time of death is important because of survivorship clauses in wills.

For the millennia, human has struggled with the concept and criteria of death, and thus, the line between life and death continues to be debated. The profound changes caused by the life support in organ failure, organ substitution technology, and transplantation still continue to challenge our notions of life and death [1]. Despite scientific progress in the last few decades, there remain big variations in the diagnosis criteria applied in each country with legal regulations resulting in misunderstandings among the public and health care professionals. Since the ample decades, the academic literature and the media have raised the voice in alarming language in issues of death determination and dead donation practices [2]. Difficulty arises to distinguish valid scientific critique from those criticisms supported by the fear of death itself, mistaken diagnosis or a premature declaration of death, or the fear of retrieving organs from the living.

The challenges in discussions about death are complex due to philosophical, religious, and cultural differences in the concept and definitions of death; debate about ethics, law, and religion; problems in performing research and the resultant shortfall in information and evidence on various aspects of the dying process; dispute in the validity of death determination practices; lack of understanding and/or awareness by general public and health professionals; last but not the least the emotionally charged nature of the subject matter. There are plentiful ways of dying but just one way to be dead. Hence, the baseline determination of death criteria should be rigorous, global, and acceptable for medical practice worldwide, while remaining respectful of diversities. International consensus on the clinical criteria for the death determination is of central importance to preserve public trust and promote ethical practices that respect the fundamental rights of people and promote quality health services [3].

In medical practice and law, the separation between being alive and dead should not be ambiguous. It designates the moments that follow events such as no medical or legal need to maintain resuscitation or life support, loss of personhood and individual rights, decedent's legal will execution, disposal of the estate, life insurance

* McWhirter N. The Guinness Book of World Records. New York: Bantam Books; 1981. p. 42 [citing the case of Elaine Esposito who lapsed into coma following surgery on August 6, 1941 and died on November 25, 1978, 37 years and 111 days later]

settlement, burial or cremation of the body for final disposition, and religious or social ceremonies to mark the end of a life [4]. Dying is not an event rather a process, which affects various functions of the body at different rates of decay. The physician must confirm the moment along this process that there is permanence and death can be accurately declared [5]. Biological criteria of death are associated with biological features and irreversible loss of certain cognitive capabilities [6]. A patient could be declared dead legally as lack of brain function and may still have a heartbeat when on a mechanical ventilator. Though there is no justification in supporting the ventilation of a dead person, withdrawing the ventilator before the legal criteria of death may involve the doctor in both civil and criminal proceedings. The legitimate moment of death could be a wide range of time after the death has actually occurred. Many accident victims actually died at the scene of the accident but were declared dead officially on arrival at a hospital.

The scientific, biological, and medical aspects of the determination of death are still controversial. Certain ancillary and/or complementary laboratory tests could also be useful in situations where clinical testing cannot be executed or if confounding or special conditions are present. It had been recognized that there are limitations to the utilization of a number of these tests and further work will confirm the reliability of these tests. Death is a biological phenomenon, with profound social, religious, and psychological traditions, but very little background experience and available scientific information. The understanding of the biological aspect has gradually developed and strengthened as a direct result of technology, cell biology, organ donation, and transplantation, but was inadequately adjust in law, health policy, and bioethical discourse. Organ donation has forced the understanding of moment of death and acceptance or persisting controversy of where that line is.

It is urgent time demanding notion to adopt a minimum determination of death criteria to be acceptable for medical practice worldwide to achieve international consensus on clinical criteria to maintain public trust and promote ethical practices.

2. Philosophical, religious, and bioethical discourse/debate

The concepts and practices of death undoubtedly are influenced by values and social practice. The definition of death affects not only that consider to count as death, but also questions of grieving, medical treatment, asset disposal, organ donation, and a myriad of other legal and ethical issues [7].

The philosophical investigation of human death has focused on some overarching questions—What is human death? The conceptualization (definition) of death is the answer to this ontological question that defines death as the irreversible cessation of organismic functioning along with the irreversible loss of personhood. Next question, how can be determine that death has occurred? The answer is epistemological one, which furnishes both the *general standard* (criterion) for determining that death has occurred and *specific clinical tests* to show whether the standard has been met in a given case. Examples are traditional cardiopulmonary standard or neurological standard [8].

Finally, how do the deaths relate, conceptually, to the essence and identity as human persons? The metaphysics of the body and soul does so in terms of the logical dualism between the material body and consciousness or the immaterial mind. In the philosophy of mind, mental phenomena are nonphysical and thus distinct and separable from the body. The dualism of body and soul/mind suggests that while being a person is, undoubtedly, a matter of having a biologically human body. The existence of a person entails the presence of a thinking being, which has reason and reflection, and can consider itself as itself, in different times and places. The

individual identity of psychological persons is dependent on the brains' neurophysiology [9]. The brain death need not be considered as biological death rather a proxy for the loss of individual identity, that is, personhood [10]. When a person has died, it does not merely mean that some biological entity no longer functions. It means some unique mind or person, realized as a cognitive or psychological entity, has ceased to exist. The personhood admits of application of the terms life and death. It has been exceedingly rare for the demise of a biological human organism to take place sometime after the death of a person. Artificial life support can maintain the biological life of an individual in the absence of their continued psychological existence. Such brain dead individuals have been considered living cadavers and twice dead [11]. Human life is operationally defined by the onset and cessation of organismal function [12]. There are two different meanings to human death being alive and having a life, the notion of personhood allows us to focus on the autobiographical meaning of death—the loss of a person [13].

Other philosophical questions—When does a human being die? Is the organismic and denouement conception of death have any practical use? Schofield et al. present a definition of death focused on the final denouement of human beings as biological organisms. According to their view, the moment of death is the last process in bodily functions that maintain homeostasis and finally ceases [14]. Reducing death to the biological denies an important characteristic of being human, intellectual, or psychological nature. The conception of death acknowledges the cognitive aspect of human existence, at the same time, accommodating embodiment, that we both have and are biological bodies [15].

Generally, people believe that death terminates the whole existence of a person. According to Christians' belief, death puts an end to human existence on earth but does not end existence, instead opens an entrance into another sphere where existence continues either in heaven or hell after the final judgment that everybody will face it. Death is considered *a type of sleep* as the sleeper does not cease to exist while his body sleeps. Therefore, a dead person continues to exist despite the absence from the region in which those who remain can communicate with him. Sleep is understood to be temporary, but the unconsciousness in the dead is seen to be permanent [16]. Muslims and Jews have the same belief. The Quranic verses distinguish life and death, as sleep is a form of reversible unconsciousness (life) comparable to death as irreversible unconsciousness, both are the commandment of Almighty creator of the universe. With the moment of this commandment, the total integrating and coordinating mechanism of the human body is irreversibly lost and the person has no relation with this world. Finally, all religious beliefs support that death is the separation of the soul from the body. Plato defines death, as nothing else but the separation from each other of two things, soul and body [17].

Life is fundamentally grounded on the continuation of individual and collective cell function, dependent on the supply of nutrients and oxygen. Cell biology has exhibited that a layer of human cells, separated from the human organism, could also be grown in laboratory culture pending till bathed in a steady supply of nutrients and oxygen. The human being, a complex package of trillions of cells organized into organ systems, requires a cardiopulmonary delivery system for oxygen and nutrients to reach the cells. The development and evolution of modern cardiopulmonary resuscitation evolving into cardiopulmonary support technologies have been important advances informing our concepts of life and death.

The introduction of advanced medical technology poses new problems for the old standards that constitute death. The values automatically shape thinking of the death of a person, not merely a descriptive, scientific concept, but unequivocally contain evaluative content. The changing frontiers of the death drive to confront basic questions of persons and values that will adapt to address future questions.

It is vital to examine the evaluative content of concepts and practices relating to death, and reflects on what it is that we value or should value in persons. The philosophical definitions of death in the absence of indisputable objective signs of death should be considered, loss of integrative functioning of the whole organism, failure to engage the environment spontaneously by respiration, loss of consciousness and sentiency, and the separation of some vital principles from the body.

The neurological criteria for death represent an interesting advance in the ways of responding to changes in death and dying. The development of medical technology and life support techniques insist increasingly on precise notions to identify the most important aspect of neurological lives. However, the whole brain standard of death suffices in the vast majority of cases, but does not fully line up the value in persons. Time has come to decide the position of the current brain death standard as it mismatch with the values and negative consequences in determining death and in organ donation. Advances in technologies seem as if they will inevitably make this question inescapable. The prominence of ***biomedical criteria*** relying on brain death reduces the impact of metaphysical, anthropological, psychosocial, cultural, religious, and legal aspects disclosing the real value and essence of human life [6]. Should we retain the current brain death standard despite its mismatch with our values and despite negative consequences in determining death and in organ donation? Is a human being with total brain failure dead?

3. Definition of death

Ideally, the definition of death would link the concept of life or death with its clinical manifestations as closely as possible that fall in both two categories, the *philosophical* (conceptual), the understanding of essential differences between life and death, and *empirical*, which is to determine clinical signs, tests, or criteria that separate life and death most accurately.

Death is the transition from being a living mortal organism to being something that, though dead, retains a physical continuity with the once-living organism. Death is a process involving the cessation of physiological functions and the determination of death is the final event in that process. Death is a gradual process at the cellular level with tissues varying in their ability to withstand deprivation of oxygen. A distinction is now being made between death at the cellular and tissue levels and death of the person. Sydney declaration states, clinically, death lies not in the preservation of isolated cells but in the fate of a person. Korein's view of the life of the multicellular organism as a whole could no longer be explained in terms of a cellular task alone. The life of a typical unicellular organism encompasses fundamental tasks of the metabolic and reproductive attributes of a particular organism, empowering it to amplify in a direction of decreased entropy production (bacteria, amoeba, or zygote). In a multicellular organism, a large mass of cells could be alive but this does not indicate that the organism as a whole was alive. Machado refused the hypothesis that an explanation of death should include the function that contributes to the key human attributes and the highest level of control in the hierarchy of integrating functions within the human organism [18–24].

The full version of death includes three unique ingredients such as the definition of death, yardstick of brain death, and the tests to prove that the standard has been satisfied. The definition of death is typically a philosophical task, while the criteria and tests are medical tasks. Particular standards and tests must match with a given definition. The definition must represent attributes that are so important and significant to a living entity that its absence is designate death [25, 26]. The nonfunctioning entire brain provokes the permanent cessation of the functioning of the organism as a whole.

Biologically death is defined as the extinction of biological properties of life. Human death can be defined as the irreversible cessation of three interdependent and interlink vital functions of the body—the tripod of life (heart, lung, and brain). Another way death can be defined as a person is said to be dead, if he cannot take up spontaneous respiration or maintain circulation. There is growing medical consensus in a unifying concept of human death, which involves the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe.

Uniform determination of death (UDDA) act defines death as, an individual who has sustained either irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all the functions of the entire brain, including the brain stem, is dead. Montreal forum defines death as the irreversible loss of the capability for consciousness and loss of all brainstem functions. That could result as a consequence of permanent stoppage of circulation and/or after catastrophic brain injury. In the determination of death, "permanent" refers to the cessation of function that cannot resume automatically even not be restored through intervention. The determination of death must be made in accordance with accepted medical standards.

4. Pathophysiology in death process: brain failure and ventilator support

The presence of the two vital functions, circulation and respiration in a body, is a sure sign of life. The patient who was diagnosed with entire brain failure and has been pronounced dead the vital functions are dependent on external support from the ventilator. The supporter of neurological standard designates these apparent signs of life are artifacts of the mechanical support that conceal the very fact that death has already occurred. To judge that logic, the essential facts of mechanical assistance for these vital functions be achieved if the interrelationship of three-body systems involved in breathing and circulation is understood. The three systems are the heart and circulatory system, the lungs and respiratory system, and the central nervous system. The pathophysiological processes that eventually end in mortal condition, *total brain failure* engage not only the central nervous system but also the circulatory and respiratory systems.

The prime functions of respiration are ventilation and diffusion. The ventilation involves both inhalation and exhalation; the diffusion involves the exchange of oxygen and carbon dioxide between atmospheric air and blood. The respiratory system brings atmospheric air by inhaling process to the alveoli where oxygen from the atmospheric air is able to move into the blood by the process of diffusion. The exhaling process of breathing facilitates to rid the body of the waste products—carbon dioxide. The walls of the alveoli are extremely thin, formed to facilitate the diffusion of gases between the sacs and the blood vessels. Oxygen is essential to the continued metabolic work of the trillions of cells in the body. The absence of an endless delivery of oxygen, brought into the body through inhalations and transported to the tissues by the *circulatory* system, the cells, tissues, and organs of the body would stop functioning. The gas exchange is facilitated by the contraction and the relaxation of the muscles of respiration and the diffusion of gases into the blood across the lining of the tiny alveoli.

The CNS plays a crucial role in maintaining an organism's vital functions. The reticular activating system of the brainstem is also critical to the organism's conscious life, essential for maintaining a state of wakefulness, which is a prerequisite for any of the activities associated with consciousness. The contraction of the

muscles of respiration is brought about by a signal sent from the respiratory center located at the brainstem. A relatively high level of CO_2 in the blood stimulates the respiratory center to send a signal to the muscles of respiration, which excites them to contract. For life to continue, the CO_2 must be expelled and new oxygen brought in. Other parts of the CNS also be involved in signaling the muscles of respiration to contract, like *conscious breathing* where a person deliberately controls the depth and pace of breathing or *without conscious effort* as during physical exercise. If the respiratory centers of the brainstem are disabled, the organism will not make any respiratory effort. The chest will remain absolutely immobile and the body's need for oxygen will go unanswered [27].

To prevent the death of the organism, some external device (mechanical ventilator) for the breathing process is essential. The mechanical ventilator works by altering the pressure in the lung cavities in order that oxygen-rich atmospheric air will travel down and CO_2-rich air will travel back up the respiratory tree. Gas exchange in the lungs will be of no benefit to the patient unless the blood is kept moving as well. Incoming oxygen must be delivered to tissues that required it, and accumulating carbon dioxide must be a shift to the lungs for expulsion from the body. Hence, a ventilator will help the patient as long as another vital system is functional, constituting the heart (working as a pump) and network of arteries, veins, and capillaries. The movement of blood occurs only within the body, whereas the movement of air is an exchange between the body and the surrounding atmosphere. Another relevant rationale of external support of vital systems is the indisputable fact that there is no part of the CNS that is absolutely essential for heart contractions within the way as the respiratory center in the brainstem is unconditionally essential in breathing. The heart is the most essential active part of the circulatory system and the vessels of circulation, being rigid plumbing lines that passively convey blood, pumped by the heart, are living tissues that undergo changes (some driven by CNS) to sustain a proper blood pressure. Patients of ventilator support must also be given drugs to maintain the blood pressure in a healthy range. Ventilator support designates the external supports of vital functions of breathing and circulation, in lieu of breathing effort of organism, stimulated by the respiratory centers of CNS, an external device moves the lungs and facilitates the inflow and outflow of needed air. It offers the heart muscle still to function, as the myocardium, like other cells in the body, needs oxygen to stay alive. The argument for the neurological standard of determination of death begins with facts that the respiratory motion supported in this way is not in itself a symbol of life, rather an artifact of technological intervention. Neither a beating heart, in this instance, a symbol of life, or merely the continuation of a spontaneous process would quickly cease if the ventilator is withdrawn [27].

Loss of the ability to breathe is not a sufficient condition for declaring that an individual has died, along with other functions indicative of life must be lost and functional losses must be irreversible. The inability to breathe automatically is insufficient for pronouncing death can often easily be dispelled by considering neurological injury that deprives a patient of the power to breathe and yet leave untouched the ability to continue activities dependent on other parts of the CNS. Patients with high spinal cord injuries remain awake and alert but dependent upon ventilators for respiratory support. Moreover, deprivation of all functions of the CNS is not a sufficient criterion for declaring death if this stoppage of function is not permanent. There are critical care cases that reveal the significance of this criterion such as a patient in a deep, nonbreathing (apneic) coma during a critical emergency and therefore assist in ventilator allowing time for CNS functions to return. Sometimes a full recovery of CNS functions happens, though the functions that return will only be enough to abandon the patient in a vegetative state and will

be labeled as a persistent vegetative state PVS.[†] The deep, nonbreathing coma that the patient was in prior to waking into the vegetative state could not have been dead since the loss of functions proved to be reversible.

5. Historical landmark in biomedical aspect of death determination

5.1 Medieval landmark: transition from heart to brain

Humans have long used criteria and technology to assist in the diagnosis of death. The link between breath and life is equally as ancient and found in both Genesis (2:7) and the Qur'an (32:9). Somatic criteria, such as the presence of decomposition and rigor mortis, are the oldest in human history. Over 800 years ago, when Maimonides codified the diagnosis of death as the absence of the heartbeat and respiration with cooling of the body [28], he was likely documenting a standard used from down of civilization.

In the eighteenth century, the physician was confirmed about death if the heart and lungs break off, but lacked adequate tests to certify it. In the twentieth century, the moment of death became less clear, and thus, the tests physicians had finally perfected proved insufficient. Historically, until the early twentieth century, physicians' inexperience in human anatomy and physiology left them poorly equipped to accurately test for death. From the eighteenth through the mid-twentieth centuries, a person was declared dead when the heart stopped beating and lungs ceased to function. In the early part of the twentieth century, while the standard to check death was well established, the understanding of when the death occurred became the subject of great debate. The fear of premature burial was replaced by the fear of apparent death sustained by life support systems. These issues reach a climax in the latter part of the twentieth century when the cardiorespiratory definition of death was reevaluated and a novice addition of brain death was introduced. Intensifying new questions as to the moment of death, the brain death criterion demands further revision of the empirical tests. The nature of death, however, does not lend itself to one discipline rather considers metaphysics, sociology, theology, and medicine. Historically, the irreversible stoppage of heart and lung functions constituted death as the absence of heart and lung activity immediately leading to failure of the entire organism. It has become apparent that cardiac and respiratory activities were significant for separating the living from the dead. The moment of death was firmly estimated but the task of confirming criteria to check for irreversible quiescence of functions proved more challenging and often had catastrophic consequences. A consensus emerged that once the heart and lungs ceased to function the person was dead, although the empirical criteria to test for death were suspect. Because of this critical divide between theory and practice, instances of premature burial occurred. To safeguard premature burial date back to antiquity with the Thracians, Romans, and Greeks, each waited 3 days for putrefaction to start before burying their dead. The Romans took a more extreme approach by amputation of a finger to ascertain if the stump bled, in addition to calling out the person's name three times while on the funeral pyre. Hence, the premature burial was a great worry, though it did not attain climax until the eighteenth century, accelerated by the intellectual climate. The knowledge and scientific revolution instituted a radical change in the insight of life and death [29].

[†] Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet. 1972;1(7753):734-737

Belief in the afterlife was not as important as life here due to the works of Bacon, Descartes, and Galileo, which emphasized the notion that life might be improved if not perfected by scientific manipulation. There is little practical obligation to worry oneself with an afterlife if this life could be manipulated by the art of medicine. Revulsion (drawing of disease) by the dissection of cadaver found in the sixteenth and seventeenth centuries as the study of human anatomy revealed the secrets of the *belle mécanique*, or the beautiful machine [30]. Fears of premature burial appear to have culminated in the eighteenth century, when George Washington made his dying request and Jean-Jacques Winslow in 1740 famously stated that putrefaction is the only sure sign of death. In 1833, Dungson also voiced commencement of putrefaction as a certain sign of real death [31]. Traditionally, the physician uses the basic cardiopulmonary standards as heart or lung functioning criteria to determine the death. The physicians palpate pulse, listen for breathing, hold a mirror in front of the nose to test for condensation and look if the pupils were fixed. William Harvey, in seventeenth century, first described the circulation of blood and the function of the heart and under this concept, death was when the heart and circulation have stopped. Ibn al-Nafīs (died 1288), an Arab physician, wrote about pulmonary circulation 300 years before it was discovered in Europe [32–35].

During this era, fear for early burial was so prominent that led to the establishment of waiting mortuaries and security coffins with alarm mechanisms and permanent air supply. The "Academy of sciences prize" was awarded in 1846 to Dr. Eugene Bouchut for his best work on the "signs of death and the means of avoiding premature burials." He suggested the utilization of the stethoscope, invented in 1819 by Laennec, as a technological aid to diagnose death. Other popular practices for death determination were inserting leeches near the anus, applying specially designed pincers to the nipples, or piercing the heart with a long needle with a flag at the end, which wave if the heart is still beating. Bouchut suggested that a person could be declared dead if a heartbeat was absent for 2 min. He extended the period to 5 min, in the face of opposition [36–39]. Case reports from physicians (Harvey Cushing) writing around the beginning of the twentieth century had evident that patients of cerebral pathology would die from respiratory arrest and subsequent circulatory collapse. Loss of electrical activity in the brain and cerebral circulatory arrest might signify human death that was evident in subsequent decades. The advent of mechanical ventilation, halting the inevitable circulatory collapse that follows the cessation of spontaneous respiration with the advent of mechanical ventilation, and the relevance to diagnosing death using neurological standard were understood.

In 1959, two historical landmarks were published, Mollaret and Goulon proposed the term *coma de´passe´* for an irreversible state of coma and apnea, and also, Pierre Wertheimer's group, a few months earlier, proposed neurological standard for death determination, that is, *death of the nervous system* [40, 41]. Those standards are practiced widely as an indicator of medical futility and a point at which ventilation might be stopped. Using neurological criteria, Belgian surgeon Guy Alexandre carried out the first transplantation from a heart-beating donor in 1963 and Christiana Barnard performed the first heart transplantation in 1967, after DCD who satisfied the criteria for coma de´passe´ [40].

5.2 Papal allocution (1957): prolongation of life

A group of anesthesiologists observed problems of sustaining the body alive in the absence of total brain function. This problem was presented to Pope Pius XII and resulted in the publication of a papal allocution describing that *the death* declaration *was not the province of the church*. Acknowledged, *it remains for the doctor to* offer *a*

transparent *and precise definition of death and* therefore, *the moment of death*. Another important point in the relation of the "prolongation of life" was that death should not be opposed by extraordinary means in hopeless conditions, though precise phenomena of hopelessness and extraordinary were not stated. Thus, in such hopeless cases resuscitation could be discontinued and death be unopposed [42].

The papal allocution culminate research, by three categories of French neurologists and neurophysiologists during 1959, separately studied comatose and apneic patients separately, narrated terms death of the "systema nervosum and coma de´passe´" translated as beyond coma or ultra-coma and subsequently by others as irreversible coma. These patients were respirator dependent, in an unresponsive coma, and areflexive. EEG and deep intracranial electrical activity were entirely absent. The investigators' conclusion was that the brains of these patients were irreversibly dysfunctional. The WMA ethical committee and its council undertake dialogue and conference on death, 2 years earlier the first heart transplant by Christian Barnard in 1967. Wijdicks wrote that the first idea for the formation of the Harvard committee was recorded in a letter from Henry Beecher to Robert H. Ebert in September 1967. The Sydney and Harvard committees worked in parallel for several months, without either being aware of the other's work [41–45].

5.3 Harvard Ad Hoc committee report and Sydney declaration: new definition

The year 1968 was a crucial time for defining human death on the neurological ground and a milestone event in the history of medical science. On August 5, 1968, the Ad Hoc committee of the Harvard medical school to examine the definition of brain death published a report, as ***irreversible coma***, in the JAMA [46]. On the same day, the 22nd World Medical Assembly, meeting announced the Declaration of Sydney [47–49], a pronouncement on death that is less often quoted because it was overshadowed by the impact of the Harvard report. The delegates from 26 countries of 64 WMA member nations met in Sydney, Australia, to hold the 22nd assembly. The WMA had been worried about a new definition of death, to formulate a report of death under the new circumstances in an epoch of advances in resuscitation, and the increasing need to find organs for transplantation. The concept of brain death was formulated in this landmark report as irreversible coma. Though brain death has been widely accepted for the determination of death globally, many controversies yet to be settled. The concept evolved as a result of the convergence of several parallel developments including advances in resuscitation and critical care, research into underlying physiology of consciousness, medical futility, and ethics in end-life-care.

Since 1968, the concept of brain death has been extensively analyzed, debated, and reworked. Still, there remain much misunderstanding and confusion, especially for the general public [50]. The Declaration of Sydney touched on key philosophical issues on human death. It proclaimed that in most situations physicians could diagnose death by the classical cardiorespiratory criteria. In spite of this, two modern practices in medicine force them to revise the time of death: first the ability to maintain circulation by artificial means and second the use of cadaver organs for transplantation. The essential public addresses death as a progressive process at the cellular level with tissues varying in their capability to cope with deprivation of oxygen, but clinically death "lies not in the preservation of isolated cells but in the fate of a person." Also, it is described that the death determination must be grounded on clinical judgment, supplemented if necessary by a number of diagnostic aids, emphasizing the EEG. Nonetheless, it asserted that the overall judgment of the physician could not be replaced by any ancillary test. The declaration went further, proposing a more philosophical and conceptual explanation about

the relationship between death and the fate of a person. The Harvard committee did not provide a clear concept of death but emphasized a clinical explanation of brain death, describing in detail the anatomical substratum and tests. The Sydney declaration did not use the term brain death but declared the clinical judgment for death determination and the Harvard committee, although mentioned the term brain death, finally select irreversible coma along with a detailed set of clinical criteria for death declaration. Both the Sydney and the Harvard committees suggest the use of EEG. For the purpose of the death diagnosis and transplantation, the Sydney declaration advocates two or more physicians not involved in transplantation should make the diagnosis, while the Harvard committee voiced that the death declaration should be made first, and then, physicians not involved in the transplantation procedure should be the one to turn off the respirator. Both committees justify a legal regulation of this issue [49]. Sydney declaration was amended at 35th WMA, by the addition of a key point declaring that "It is essential to determine the irreversible cessation of all functions of the whole brain, including the brain stem" for diagnosis of brain death but the EEG was not mentioned and no other issues were modified [49, 50].

5.4 President's commission report on medical, legal, and ethical issues in the determination of death: definition of death and UDDA

In July 1981, the President commission for the study of ethical problems in medicine and behavioral research published a report, *defining death*, to the President, Congress, and the relevant US government departments. It proclaimed that a person is dead, who has experienced either *irreversible stoppage of circulatory and respiratory functions*, or *irreversible cessation of all functions of the whole brain, including brain stem*. The death determination must be practiced in accordance with accepted medical standards. President's Commission report permitted consolidation of the whole-brain criterion of death [51].

A scientific basis was suggested to justify brain death with the theory of the brain as the central integrator of the body. According to this theory, the organism becomes a rapidly disintegrating collection of organs following the brain death (BD). Consequently, the concept of BD is not only an ethical and/or social concept or a matter of values, rather a matter of scientific facts such as irreversible stoppage of functioning of the organism as a whole is death. The guiding principles of irreversible cessations of functioning of the entire brain are absolutely correlated with the permanent cessation of functioning of the organism as a whole as the brain is necessary for the functioning of the organism. The brain integrates, generates, interrelates, and controls complex bodily activities. A patient on a ventilator with entirely destroyed brain is merely a group of artificially sustained subsystems since the organism as a whole has ceased to function. President's Commission report also supports that rationale, convincing the gravity of the brain and recognized the profound instability of the brain-dead organism. In adults who have an irreversible stoppage of the whole brain's function, the mechanically generated functioning could exist only for a limited time as the heart usually stops beating within 2–10 days [51].

The enabling legislation for the President's Commission directs it to study the ethical and legal implications of the matter of defining death, including the probability of developing a uniform definition of death [51]. The central conclusions were that the recent developments in medical treatment necessitate a restatement of the standards traditionally recognized for determining that death has occurred and such a restatement ought preferably to be a matter of statutory law, which should be uniform among all the states. The definition embodied in the statute ought to

address general physiological standards instead of medical criteria and tests, which will change with advances in biomedical knowledge and refinements in technique. The death is a unique episode that could accurately be confirmed either on the traditional grounds of permanent cessation of heart and lung functions or on the basis of permanent loss of functions of the entire brain. Any statutory definition must be separate and distinct from provisions governing the donation of cadaver organs and any legal rules on decisions to terminate life-sustaining treatment. American Bar Association, American Medical Association, and the National conference of commissioners on uniform state laws together have declared the statute, the Uniform Determination of Death Act (UDDA) affirmed: "an individual is dead who has **sustained** either, *the irreversible cessation of circulatory and respiratory functions*, or *irreversible cessation of all functions of the entire brain, including the brain stem*." A determination of death must be made in accordance with the accepted medical standards [51].

The UDDA is a statute, to address the societal problem created in the mid-twentieth century, due to the development of mechanical ventilation and other organ-sustaining technologies, to support permanently brain-injured individuals. The justification of the UDDA was to establish a uniform definition of death, determined by *acceptable medical standards*, that was transparent and socially accepted. The President's Commission and the UDDA considered death to be a unique episode in spite of causation, resulting from either irreversible failure of the brain or circulatory function. The act acknowledged the biological facts of universal applicability while seeking to safeguard patients against ill-advised idiosyncratic pronouncements of death. The UDDA viewpoint was supported by the majority of medical and legal authorities, the original UDDA wording also supported by the AAN. The neurologic insults may cause temporary stoppage of multiple brain functions, leading to disorders of consciousness, and the irreversibility component for the brain death criteria requires that these functions have ceased permanently, with no hope of resumption through clinical intervention or auto-resuscitation. Several medical associations support the UDDA definition of death and have participated in guideline development pertaining to the establishment of brain death in adults and children. A patient declared dead legally by considering neurologic criteria in all the state of USA except the state of New Jersey, however, allows for religious exemptions to the declaration of brain death if family members object. In such cases, death is not declared until the patient has met cardiopulmonary criteria for death [52–55].

5.5 Task force recommendations (1987): the guidelines for the diagnosis of brain death in infants and children (pediatrics guideline)

In the executive summary update of task force recommendations, declare requisite for the diagnosis of brain death in children of two neurologic examinations is performed by two independent physicians and two apnea tests, both of which may be organized by the physician managing ventilator care [56, 57]. Examinations should follow an observation period of 24 hours for neonates less than 30 days old and 12 hours for older infants and children up to age 18. It is significant to note that there may be institutional variance in the way these criteria are interpreted, and pediatricians may adapt their brain death testing methods to take into account the age-related anatomical and physiological differences between neonates, infants, and children. Parents and other family members of children undergoing brain death testing may require close attention and additional support [58, 59]. The pediatric guidelines were updated in 2011 by the American Academy of Pediatrics. A recent study reveals widespread disparities in adherence to the guidelines nationwide. It is essential to follow a standardized process to ensure accuracy in the diagnosis and inconsistencies in

diagnosis could lead to false-positive brain death determinations, which could erode the public trust in the ability of physicians to declare death [58–60].

5.6 White paper on controversies of determination of death by president council of bioethics: total brain failure (2008)

In December 2008, the President's council on bioethics published a white paper (controversies in the determination of death) in which the neurological standard was carefully reexamined [27]. The council built the insight in biological reality by appropriately describing the clinical and pathophysiological understanding of brain death, which offers substantial reassurance to the ultimate validity of the neurological standard. It effectively gives a new foundation to the justification for the neurological standard of death. The council strongly agreed that "*Relaxation of the DDR is a morally unacceptable and logically specious way to deal with the uncertainties of the criteria for the death of the donor*."

The council works was a historical decision that answers lot of *controversies and philosophical debate* in light of sound biological and pathophysiological evidence; debate on several controversies in the determination of death includes those arising in the context of controlled DCD with a primary focus on the clinical and ethical validity of neurological standard; controlled DCD is analyzed and the traditional cardiopulmonary criteria, also voiced concerns about the difficulty of safeguarding adequate end-of-life care for the patient-donor. The principal argument was—Does a diagnosis of *whole brain death* mean that a human being is dead? In other words, does the neurological standard rest on a sound biological and philosophical basis? [27].

Whether a patient in the condition of total brain failure is actually dead and can it be said with sufficient certainty to ground a course of action as the mortal remains of a human being. To ascertain those, up to this time, two facts about the diagnosis of total brain failure have been taken to provide basic support for a declaration of death: first, that the body of a patient with *total brain failure* diagnosis is no longer a *somatically consolidated whole*, and, second, that the capacity of the patient to sustain *circulation* will cease within a definite span of time. Another dispute, a patient with total brain failure is no longer able to carry out the basic work of a living organism. The patient has lost permanently the openness to the surrounding environment and the ability and drive to act on this environment on his own behalf. The respiratory function and cell metabolism sustained by mechanical ventilation are not due to *spontaneous* respiration. The council on bioethics acknowledges that such interventions with mechanical ventilation may preserve certain integrative bodily functions in patients declared dead by neurologic criteria, and such integration is not enough to define these patients as living. Patients who experience the neurologic criteria for brain death can no longer conduct the definitive work of a living organism, which is to be receptive to and act upon its environment in order to acquire the needs to preserve itself, such as breathing spontaneously, withdrawing from pain, or sleeping and waking. While such behaviors do not justify self-consciousness, they verify that the organism is alive. However, the patients kept alive *artificially*, by pacemakers, defibrillators, vasopressors, ventricular assist devices, artificial nutrition, and hydration, are not, by that fact alone, considered to be *dead*. A living organism participates in self-sustaining, need-driven activities essential to and constitutive of its trading with the surrounding world. These activities are genuine signs of active and existing life. A judgment that the organism as a whole has died can be made with confidence if these signs are lost and the activities had stopped.

Another view of the neurological standard was also pointed within the council for certainty about the vital status of patients with total brain failure, the only rational and defensible conclusion of such patients are severely injured, but not yet

dead. Hence, only the traditional signs of permanent cessation of heart and lung function should be used to declare a patient dead. Accordingly, medical interventions for patients with total brain failure should be withdrawn only after they have been judged to be *futile*, in the sense of medically ineffective and non-beneficial to patients and disproportionately burdensome. The judgment must be done on the basis of ethical grounds considering the whole aspect of the particular patient and not merely the biological facts of the patient's condition. Then, the interventions can and should be withdrawn so that the natural course of the patient's injury can reach its inevitable terminus. Preparation for burial or for organ procurement is morally valid only when medical intervention has been judged as futile and the heart of the patient has stopped beating [27].

The understanding of medical futility [61, 62] has been developed in several papers by Edmund D. Pellegrino. Futility is the condition of a patient's disease, which is beyond medical rescue, such as beyond the powers of medical technology to help. Clinical futility is present when any medical intervention is considered as ineffective, non-beneficial, and disproportionately burdensome for the patient. The clinical judgments of the futility of a given therapeutic intervention involve a rational balancing of three factors: efficacy of the given intervention, the purpose of which doctor alone can make; second, the advantage of that intervention, the patients and/or their surrogates can make; and third, the burdens of the intervention (cost, discomfort, pain, or inconvenience), jointly assessed by both physicians and patients and/or their surrogates. Adjusting the relationship among those three criteria is at the heart of prudent, precautionary, and proportionate action [27].

Lastly, the council members on bioethics had opined that the current neurological standard for declaring death, grounded in a careful diagnosis of total brain failure, is biologically and philosophically defensible. The council also concluded that, *in an issue of organ transplantation, determining death and procuring organs should be addressed separately. The questions about the vital status of neurologically injured individuals should be taken up prior to and apart from ethical issues in organ procurement from deceased donors*. The recommendations are: first, to reaffirm the ethical propriety of the dead donor rule (DDR); second, to reaffirm the ethical acceptability of the neurological standard as well as the cardiopulmonary standard; and third, to reject the use of patients in permanent vegetative states as organ donors. The council has concluded that the neurological standard remains valid that was adopted at the President's commission of 1981 and enacted in UDDA.

5.7 Preserving the dead donor rule

The DDR has been secured for the ethical and social acceptability of organ transplantation protocols from their primitive days. This rule demands assurance of the death of the donor as the first step in any ethically legitimate transplantation protocol (other than those involving healthy, living donors). Additionally, the death of the patient must not be accelerated, nor end-of-life care made vulnerable in any way, to accommodate the transplantation protocols [27]. No protocol can demand ethical approval without trustiness to the present rule, in any ethically legitimate transplantation protocol (other than those involving healthy, living donors).

Relaxation of the DDR is a morally and ethically inappropriate and rationally specious way to deal with the uncertainties of the standard for the death of the donor. It leaves the options of the criteria for death to individual preference, amounting to the eventual abolition of any stable criteria for death. Numerous additional dangers are the use of assisted suicide to facilitate organ donation, legitimizing the utilization of patients in permanent vegetative states or of less-than-perfect infants as donors [27]. It exposes "undeclared" patients to "presumed" consent to donation [27, 62, 63].

5.8 Montreal forum (2012): international guidelines for the determination of death

Montreal forum was formed to address the global challenge in response to the request from various countries to "WHO and Transplantation Society" to provide guidance for leading practices and health policy in death determination by neurological and/or circulatory criteria. The guidelines would promote safe practices assuring the absence of diagnostic errors in death determination, safeguarding patients and health care professionals, upgrading public and professional confidence in the dead donation process along with strengthening the availability of organs obtained by ethically legitimate donation and procurement practices. The principles adopted by the forum for discussion were the safeguarding the interests of dying patients overrides facilitating deceased donation for transplantation; task restricted to a scientific, medical, and biological basis for death determination; the principle of the "dead donor rule" applied to deceased donation practices; use of available best scientific and medical evidence for decisions; guidelines and recommendations must have utility, applicability, and be workable in a wide range of global health care practice settings. The key issues of the forum considered death as a biological event with a focus on the physiological aspect of the dying process and death determination and respectfully recognized the impact of attending religious, ethical, legal, spiritual, philosophical, and cultural aspects of death [1].

Forum outcome of the review developed some *terminologies* for clarity for debate/discussion on death. These terminologies reduce a lot of debates on death determination and arriving at a sound consensus; the second outcome was the consensus on *death and brain*, and *death and circulation* regarding illustrative examples of precondition for neurological testing, clinical and laboratory test for diagnosis of neurological and circulatory function, guidelines for declaration, neurological and circulatory sequences of dying process, integrated circulatory and neurological sequences of the dying process, minimum acceptable criteria for clinical test, apnea test and additional lab test, auto-resuscitation, circulatory arrest and brain function, and CPR and life support. These aspect created the foundation for understanding the scientific basis of death declaration and lastly *operational definition of death* with global agreement around complex practice and future research to enrich the knowledge and overcome the gaps. Finally, the forum came to a consensus on seven key areas: Death must be diagnosed on clinical standard based on direct, measurable observation or examination of the patient; physiological events of halting of circulatory and neurological functions leading to death were developed to prove the critical events occurring in a catastrophic injury or illness; clinical tests that satisfy the minimum clinical standard for the death determination were defined for both the neurological and the circulatory sequences; preconditions and confounding situations may impede or invalidate death diagnosis [1]; certain ancillary and/or complementary lab tests might be beneficial in situations where clinical testing cannot be performed or if confounding or special conditions present. Also, the drawback of using some of these tests is acknowledged and further research is recommended to identify the reliability of those tests; a precise terminology regarding death was reviewed and finalized in order to improve clarity in discussions and debate on death determination; the fundamental to define human death should be on measurable biomedical standards and authenticate movement away from anatomically based terms, brain death, or cardiac death misleading to imply the death of that organ. Priority had been placed on the stoppage of neurological or circulatory function and the predominance of brain function for determination of death [1].

The forum came to a consensus on an operational (practical and concrete) definition of human death based on measurable and observable biomedical standards that "Death occurs when there is permanent loss of capacity for consciousness and

irreversible loss of all brainstem functions." This might result from permanent stoppage of circulation and/or after catastrophic brain injury. The "permanent" refers to loss of function that cannot resume automatically and will not be returned through intervention. Death is a single phenomenon founded on stoppage of brain function (loss of capacity for consciousness and brainstem reflexes) with two mechanisms to reach that point: permanent absence of circulation or subsequent to a catastrophic brain injury—two entrances, one exit. It is understood that the overwhelming majority of death determination in the world occurs after the stoppage of circulation and usually occurs external to health care settings. In some regions, the dead donation practices include re-establishing circulation (CPR, extracorporeal organ support) following death for the preservation of organs. Future research will enrich this issue for the clarity that constitutes re-establishing circulation, physiologically meaningful circulation, circulation versus oxygenation, and distinctions between organ targeted, regional, and whole-body circulation [1, 64].

6. Variation in death determination criteria in the Asia Pacific

During the 50 years since the publication of reports on the determination of death by neurologic criteria by Harvard University and the WMA (Sydney declaration) in 1968, brain death/death on neurological criteria (BD/DNC) protocols have been developed in many countries around the world. However, some countries still do not have medical standards for BD/DNC, and there is also international and intranational variability between the protocols that do exist [65–68].

Discrepancies were noted in the studies by Wijdicks, Wahlster et al., and Chua et al. between protocols in this region in the criteria used for diagnosis of BD/DNC. Nonetheless, these studies were all limited reviews, though they addressed a number of examiners, observation time, the time between examinations, concordance/discordance with AAN—brain death/death by neurological criteria practice parameters, target value and methods of apnea testing, and requirement for ancillary testing. They did not explore the more distinct aspects of BD/DNC protocols, such as the technique used to rule out the effect of drugs on the evaluation, minimum temperature and blood pressure for an evaluation to be performed, a technique used to assess each component of the examination and findings of BD/DNC, preparation for rationale to discard apnea testing, accepted ancillary tests, need for communication with a person's family, time of death, and stopping of organ support [68]. The existence of a protocol in a given country is dependent on acceptance of BD/DNC as death, access to resources (neurosciences/critical care experts), the presence of a transplant network, and local laws. Religious beliefs markedly influence the acceptance of BD/DNC as death. Although religious views in these countries are distinct from those in the rest of the world, the diversity of political, economic, legal, social, and religious climates throughout the region mirrors that globally [65–68].

A review by Lewisa et al. in 2020 was published in a clinical neurology journal to find out the similarities and differences in the official protocols for the determination of death in Asia Pacific countries (57 of 197 UN) and concluded that protocols for conducting a BD/DNC determination vary markedly. In their report, only 24 of the 37 countries had brain death protocols (69%), but vary in definition such as whole-brain death and brain stem death; a number of examinations vary from single to double, separated by 6–48 hours; and the prerequisites, clinical examination, apnea testing procedure, and indications for/selection of ancillary tests varied. But agreed on that the damage to be irreversible or be permanent, all function/all activities are to be absent before declaring BD/DNC. Also, it is emphasized to harmonize protocols both within this region and worldwide [65–68].

7. Practical guidance for the determination of brain death

Traditionally, death occurs with the confirmation of irreversible cessation of cardiorespiratory function [3, 53–58]. The use of artificial maintenance of life support and organ transplant leads to introduce a new criterion of death determination of permanently nonfunctioning brain, called irreversible coma equated to brain death. In recent years, however, controversy has arisen about the clinical and ethical validity of the neurological standard. **WHO** in 2014 formulated up-to-date update of minimum determination of death criteria for globally acceptable medical practice while respectful to diversities that achieve international consensus on the clinical criteria of determination of death to maintain public trust and promote ethical practices that respect fundamental rights of people and minimize philosophical, ethical, and biomedical debate in the human death. This guideline of clinical criteria on the determination of death suggested that there may be various ways to determine death but there is only one way of being dead, so the two classic algorithms, the brain death and circulatory death, merge into a single endpoint identified as death and should not imply that brain death and circulatory death are two separate phenomena [3]. This guideline also prepares a workable flowchart (**Figure 1**) of **cardiocirculatory algorithm** and **neurological algorithm** to declare the death. The algorithms identify the tests that are required to be conducted at each stage of the event, but they do not specify the details on how each test should be performed, which may be a free-standing documents that do not demand cross-references to other guidelines and be applied to both adults and children, and finally, a checklist is developed to facilitate the implementation of the different components stated in the algorithms [3]. This guideline provides acceptable clinical criteria of medical practice for the determination of death and earn international consensus on death debate but did not mention the detail of the clinical examination [3]. Harvard report describes the clinical criteria, and AAN guidelines on clinical criteria on neurological standard had already been accepted globally.

AAN clinical criteria on the determination of brain death [53–56] can be considered to consist of four steps: Prerequisites, Neurological assessment (coma, absence of brain stain reflex, apnea), Ancillary test, and Documentation.

I. Prerequisites for clinical criteria of brain death determination.

A. Establish permanent and predicted explanation of coma:

- The explanation of coma is often establish by history, clinical examination, neuroimaging, and laboratory tests.

- Rule out the existence of any CNS-depressant drug effect by history, drug screen, calculation of clearance; or, if available, drug plasma levels below the therapeutic range. Prior use of hypothermia (following CPR) may delay drug metabolism. The legitimate alcohol limit for driving (blood alcohol content 0.08%) is a practical threshold below which an examination to determine brain death could adequately proceed.

- Should be no current administration or existence of neuromuscular blocking agents (train of four twitches with maximal ulnar nerve stimulation).

- Should be no critical electrolyte, acid–base, or endocrine disorder (severe acidosis or laboratory values markedly deviated from the norm).

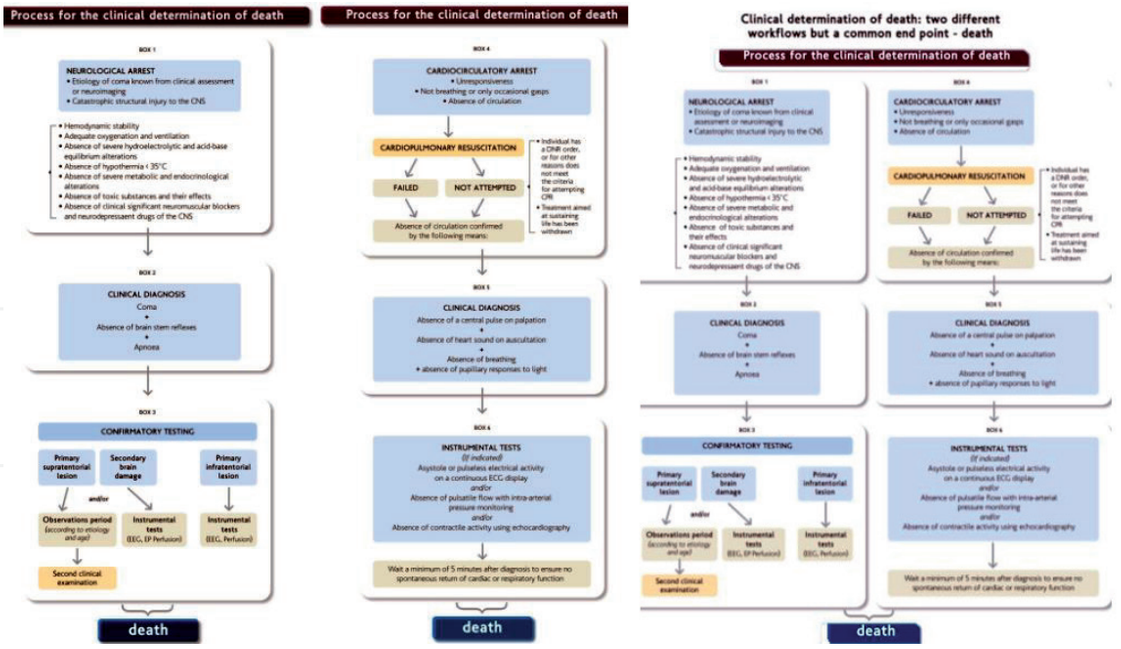

Figure 1.
Source: Ref. [3].

B. Ensure normal core temperature.

Raise the body temperature and to sustain a normal or near-normal temperature (36°C) use a warming blanket. To prevent delaying an increase in $PaCO_2$, normal or near-normal core temperature is preferred during the apnea test.

C. Ensure normal systolic blood pressure. Hypotension or hypovolemia should be corrected by vasopressors or vasopressin. Neurologic examination is commonly reliable with a systolic blood pressure ≥ 100 mm Hg.

D. Perform neurologic examination (one neurological examination is enough to declare brain death in the USA). A certain period of time has to be passed since the onset of the brain insult to rule out the possibility of recovery (usually several hours). However, some US state statutes require two examinations.

E. Legally, all physicians are authorized to determine brain death in the USA. Neurologists, neurosurgeons, and intensive care specialists may have specialized expertise. It appears rational that all physicians making a determination of brain death be absolutely familiar with brain death criteria and have demonstrated competence in this complex examination.

II. Neurological assessment for clinical criteria for brain death determination.

A. Coma:

- Profound loss of consciousness with no response to any stimuli. No evidence of responsiveness. No motor response on noxious stimuli other than spinally mediated reflexes.

B. Absence of brainstem reflexes:

- Lack of pupillary response to bright light is produced in both eyes. Usually, pupils are fixed in a midsize or dilated position (4–9 mm). Constricted pupils signify the possibility of drug intoxication. A magnifying glass can be used in doubtful cases.

- Oculocephalic testing and oculovestibular reflex testing: Absence of ocular movements. Once the integrity of the cervical spine is ensured, the head is briskly rotated horizontally and vertically. No movement of the eyes relative to head movement. The oculovestibular reflex is tested by irrigating each ear with ice water after the patency of the external auditory canal is confirmed. The head is elevated to 30°. Each external auditory canal is irrigated (one ear at a time) with approximately 50 ml of ice water. Eye movement was absent during 1 minute of observation. Both sides are tested, with an interval of several minutes.

- Absence of corneal reflex: Touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water, no eyelid movement will be demonstrated.

- Absence of facial muscle movement to a noxious stimulus: Deep pressure on the supraorbital ridge and the condyles at temporomandibular joints produce no grimacing or facial muscle movement.

- Lack of pharyngeal and tracheal reflexes. This reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device. The tracheal reflex is most reliably tested by examining the cough response to tracheal suctioning.

C. Apnea test:

Absence of a breathing drive is tested with a CO_2 challenge. Usually, a rise in $PaCO_2$ above normal levels is the typical practice but requires preparation before the test.

Prerequisites for apnea test: (1) Normotension, (2) Normothermia, (3) Euvolemia, (4) Eucapnia ($PaCO_2$ 35–45 mm Hg), (5) Lack of hypoxia, and (6) No prior evidence of CO_2 retention (COPD, excessive obesity).

Procedure:

- Ensure a systolic blood pressure ≥ 100 mm Hg, if needed by vasopressors.

- It is mandatory to pre-oxygenate with 100% oxygen for at least 10 minutes to a PaO2 > 200 mm Hg.

- Diminish frequency of ventilation to 10 breaths per minute to eucapnia.

- Diminish positive end-expiratory pressure (PEEP) to 5 cm H_2O (oxygen desaturation with decreasing PEEP suggest problems with apnea testing).

- If pulse oximetry oxygen saturation persists >95%, obtain a baseline blood gas.
- Detach the patient from the ventilator.
- Maintain oxygenation (deliver 100% O_2 at 6 L/min by endotracheal tube).
- Observe closely for 8–10 minutes for respiratory movements. Respiration may be abdominal or may include a brief gasp.
- Exclude if systolic blood pressure decreases to <90 mm Hg.
- Exclude if oxygen saturation measured by pulse oximetry is <85% for 30 seconds.
- If the respiratory drive is absent, repeat blood gas (PaO_2, $PaCO_2$, pH, bicarbonate, base excess) after approx. 8 minutes.
- The apnea test is positive if respiratory movements are absent and arterial PCO2 is ≥60 mm Hg (supports the clinical diagnosis of brain death).
- If the test is inconclusive but the patient is hemodynamically stable during the procedure, the test could be repeated for a longer period of time (10–15 minutes) after the patient is again adequately pre-oxygenated.

III. Supportive tests to diagnose brain death.

The ancillary tests such as EEG, cerebral angiography, nuclear scan, TCD, CTA, and MRI/MRA are at present used for adults in clinical practice. Three tests may be preferred such as EEG, nuclear scan, or cerebral angiogram, as the most hospital has the logistic to perform and interpret. The supportive tests can be done when there is no scope for apnea test or uncertainty exists. The ancillary tests are usually practiced to shorten the duration of the observation period. The interpretation of each of these tests requires expertise. In adults, ancillary tests are not needed for the clinical diagnosis of brain death and cannot replace a neurologic examination.

IV. Documentation of the time of death.

The moment of brain death must be documented in medical records and is the time the arterial PCO_2 reached the target value. But in patients where the apnea test is discarded, the time of death is when the ancillary test has been officially interpreted. A checklist is filled out, signed, and dated.

8. Conclusions

For the millennia, the human has fought with the concept and criteria of and the line between life and death continues to be debated. The profound changes

caused by life-sustaining technology and transplantation continue to challenge our notions of life and death. The cardiopulmonary approach is an age-old practice for the determination of death that ensures social acceptance without any debate. The public is also used to rely on the somatic standard for criteria of death such as cooling of the body, absence of breath, loss of consciousness, rigor mortis, putrefaction, and so on.

Despite scientific progress in the last few decades, there remain big variations in the diagnosis criteria applied in each country with legal regulations resulting in misunderstandings among the public and health care professionals. However, the Harvard committee in 1968 develops a set of criteria of the permanently nonfunctioning brain, called irreversible coma equated to brain death. On the same date, the WMA declared a guideline for the determination of death known as the *Sydney declaration*. These two landmarks' innovations change our notions for researching a new challenge in death. The addition of neurological criteria of death to cardiorespiratory criteria of death was a paradigm shift that evolved when patients with acute brain injury could be resuscitated in medical facilities. Brain death, defined as the irreversible cessation of all brain activities, has been included in the medical and legal definition of death for nearly 60 years.

The global philosophical, ethical, legal, and biomedical controversies of determining death due to life support, organ supports, and organ transplantation issues console us in the historic report published (1981) by President commission for the study of ethical problems in medicine and behavioral research, *defining death* that a person is dead, who has sustained either *irreversible stoppage of circulatory and respiratory functions*, or *irreversible cessation of all functions of the entire brain, including the brain stem*. The death determination must be made in accordance with the accepted medical standards [3]. Since then, the neurological standard has been accepted as one of two valid standards for determining death and has been adopted legally in many countries throughout the world. The other accepted standard is the older, traditional cardiopulmonary standard. One of these two valid standards was followed by UDDA legislation for legal criteria of determination of death. President council of bioethics (2008) also reconfirm this definition of death and controlled the DDR rule for organ transplantation purposes. They accept controlled DCD for organ transplantation purposes.

WHO in 2014 published clinical criteria on the determination of death, mentioning various ways to determine death but there is only one way of being dead, so the two classic algorithms of brain death and circulatory death merge into a single endpoint identified as death and should not imply that brain death and circulatory death are two distinct phenomena [3]. They prepare a workable flowchart of cardiocirculatory algorithm and neurological algorithm to declare death. That guideline provides a minimum determination of death criteria to be acceptable for medical practice worldwide to achieve international consensus on clinical criteria to maintain public trust and promote ethical practices that respect fundamental rights of people and minimize philosophical, ethical, and biomedical debate in the human death. The WHO clinical criteria of 2014 did not mention the detail of clinical examination. Harvard report describes the clinical criteria and AAN guidelines on clinical criteria already accepted globally.

American Association of Neurology (AAN) in 2019 validated that brain death is the irreversible loss of all functions of the entire brain and is also equivalent to circulatory death. The testing methods of brain death take into account the age-related anatomical and physiological differences between neonates, infants, and children. Parents and other family members of children undergoing brain death testing may require close attention and additional support [58, 59].

9. Further reading

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Acknowledgements

All praise to Almighty to bless me with good health to complete this chapter. Acknowledge to all staff of the Forensic Medicine department of IMC and my family member for their sincere cooperation. Special thanks to Prof. Sharfuddin Ahmed, VC of BSMMU for encouraging me to complete. Also thanks to Dr. Ferdausi Rahman for her review of some portion of scripts.

Authors' contributions

Prof. Md Shah Alam developed the conception and design of the article and drafted the manuscript, providing important intellectual content.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not applicable.

Abbreviations

AAN	American Association of Neurology
BD	brain death
CNS	central nervous system
CTA	computed tomography angiography
CDD	controlled death donor
COPD	chronic obstructive pulmonary disease
DDR	death donor rule
MRA	magnetic resonance angiogram

PVS	persistent vegetative state
TCD	transcranial Doppler
CCA	cerebral circulatory arrest
BSMMU	Bangabandhu Sheikh Mujib Medical University, Bangladesh
DNC	death on neurological criteria
UDDA	unifying determination of death act
WHO	World Health Organization
WMA	World Medical Association/World Medical Assembly

Author details

Md. Shah Alam Panna[1,2,3]

1 Department of Forensic Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

2 Department of Forensic Medicine and Toxicology, Ibrahim Medical College, Dhaka, Bangladesh

3 Department of Forensic Medicine and Toxicology, Sher-E-Bangla Medical College, Barishal, Bangladesh

*Address all correspondence to: drpanna@yahoo.com

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