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REVIEW

Management of donation after brain death (DBD) in the ICU: the potential donor is identified, what's next?

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Abstract

The success of any donation process requires that potential brain-dead donors (PBDD) are detected and referred early to professionals responsible for their evaluation and conversion to actual donors. The intensivist plays a crucial role in organ donation. However, identification and referral of PBDDs may be suboptimal in the critical care environment. Factors influencing lower rates of detection and referral include the lack of specific training and the need to provide concomitant urgent care to other critically ill patients. Excellent communication between the ICU staff and the procurement organization is necessary to ensure the optimization of both the number and quality of organs transplanted. The organ donation process has been improved over the last two decades with the involvement and commitment of many healthcare professionals. Clinical protocols have been developed and implemented to better organize the multidisciplinary approach to organ donation. In this manuscript, we aim to highlight the main steps of organ donation, taking into account the following: early identification and evaluation of the PBDD with the use of checklists; donor management, including clinical maintenance of the PBDD with high-quality intensive care to prevent graft failure in recipients and strategies for optimizing donated organs by simplified care standards, clinical guidelines and alert tools; the key role of the intensivist in the donation process with the interaction between ICU professionals and transplant coordinators, nurse protocol managers, and communication skills training; and a final remark on the importance of the development of research with further insight into brain death pathophysiology and reversible organ damage.

Keywords: Organ donation, Transplantation, Icu, Critical care, Brain death, Early goal

Introduction

Organ donation is a complex process that necessitates the involvement of many healthcare professionals. The majority of the process takes place in the intensive care unit (ICU). Once a patient has been diagnosed as brain-dead, he/she becomes a potential brain-dead donor (PBDD). From this point onwards, multiple tasks need to be completed in a rapid, structured fashion [1]. The processes of diagnosing brain death (BD), identifying the PBDD, medically managing the organ donor and procuring organs must all be fully integrated. At the same time, the donor's family requires compassionate care and support throughout. The inevitable stress to both family members and to healthcare providers can be significantly reduced by implementing an organ donation system. The Spanish system, for example, has resulted in an extremely successful transplantation program by

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focusing on healthcare provider training and professional development. In this manuscript, we aim to highlight key elements of an organ donation system including (1) early identification and evaluation of the PBDD using checklists; (2) donor management, including goal-directed protocols and strategies to optimize donated organs; (3) the key role of the intensivist in the donation process including interactions with transplant coordinators, and the provision of communication skills training; and (4) the importance of developing research into the areas of brain death pathophysiology and reversible organ damage.

Early identification and evaluation of the PBDD: the ABC approach to organ donation

The success of any organ donation system requires PBDDs to be detected early and to be referred early to professionals responsible for their evaluation and conversion to actual donors [2].

Most PBDDs are managed in the ICU where well-established referral protocols are in place [3, 4]. Here, the intensivist plays a crucial role. However, identification and referral of PBDDs may be suboptimal. Factors influencing lower rates of detection and referral include a possible lack of specific training and the need to provide concomitant urgent care to other critically ill patients [3]. Providing an easy tool to guide professionals may increase the number of patients in whom the option of donation is considered as part of end-of-life care [4, 5].

Take-home message

The success of any donation process requires that potential brain-dead donors (PBDD) are detected and referred early to professionals responsible for their evaluation and conversion to actual donors. The Intensivist plays a crucial role in organ donation.

The use of checklists has been shown to improve healthcare efficacy and safety [6]. The well-known ABC mnemonic is a good example. It reminds clinicians of the most important steps in the resuscitation of the critically ill patient (airway, breathing, circulation).

In order to improve the process of donation after brain death (DBD), we propose a similar ABC approach to organ donation: A "Aetiology of brain damage", B "Brain death alerts", C "Contraindications" (Fig. 1).

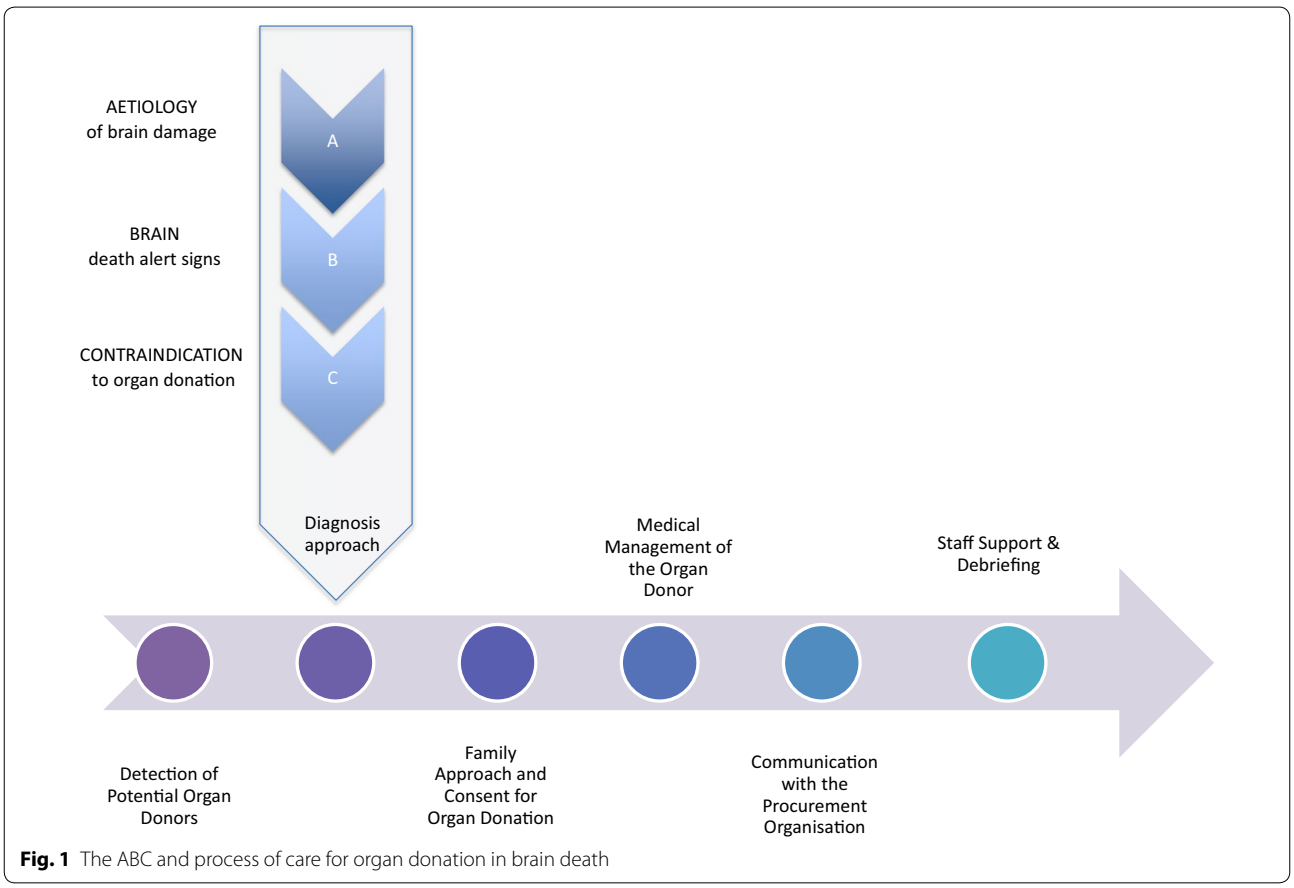

Fig. 1 The ABC and process of care for organ donation in brain death

A *Aetiology of brain damage* Knowing the cause and irreversibility of the neurological injury is necessary prior to considering any neurocritically ill patient as a PBDD. Failure to determine the aetiology of brain damage precludes the diagnosis of brain death. In the case of anoxic encephalopathy following cardiopulmonary arrest, the primary reason for the arrest (e.g. coronary artery disease, drug overdose etc.) must be investigated and determined.

B *Brain death alerts* Identification of PBDDs should occur as early as possible. However, the initiation of the formal organ donation process is controversial. In some systems, the process begins after a BD diagnosis has been confirmed (or there is a well-founded suspicion of BD) while in other systems, referral to organ donation organizations can occur before a diagnosis of BD is made (but only in the context of a devastating brain injury or where BD is imminent)

Table 1 Definitions of the critical pathway in donors after brain death. Modified from reference [44]

Possible donor
A patient with a devastating brain injury or lesion medically suitable for organ donation
Potential donor
A person whose clinical condition is suspected to fulfil brain death criteria
Eligible donor
A medically suitable person who has been declared dead based on neurologic criteria as stipulated by the law of the relevant jurisdiction
Actual donor
A consented eligible donor
In whom an operative incision was made with the intent of organ recovery for the purpose of transplantation. Or
From whom at least one organ was recovered for the purpose of transplantation
Utilized donor
Actual donor from whom at least one organ has been transplanted

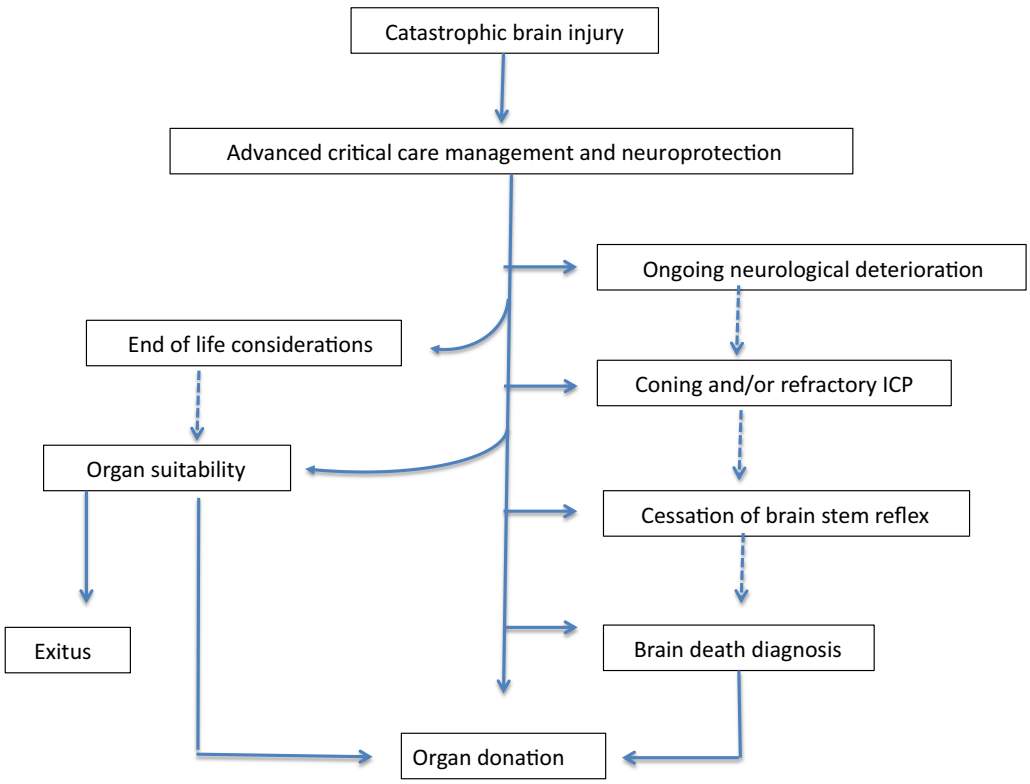

Fig. 2 Clinical pathways for organ donation after a catastrophic brain injury

[7, 8]. Not only identification but also legal certification of brain death, according to the critical pathway (Table 1 and Fig. 2), and the referral process are important to medical suitability determination as part of the definition of donor eligibility. This is of crucial importance in optimizing the medical management of donors throughout the referral process. A PBDD is not eligible for organ donation until brain death has been legally certified.

C *Contraindications to donation* The evaluation of the potential donor is usually performed by a different professional to that taking care of the patient. This is to avoid any real or perceived conflict of interest. However, the initial application of a checklist to highlight easy-to-identify medical conditions that preclude the possibility of donation can be performed by the ICU physician. This avoids the unnecessary expenditure of time and/or resources required for the in-depth evaluation of donor eligibility. This is especially the case for centres located significant distances away from procurement professionals [9, 10].

Donor management

Goal-directed protocols to increase the number of donated organs and to reduce cardiac arrests in PBDD

An adequate understanding of brain death pathophysiology and related organ damage is needed in order to tailor the treatment of circulatory instability and to optimize the timing of organ procurement. The final ischemic brainstem response to cerebral coning that precedes brain death is associated with adrenergic hyperactivity. This causes tachycardia, hypertension and an increase in pulmonary and systemic vascular resistance. This "autonomic storm" may lead to arrhythmias, myocardial ischemia and myocardial dysfunction. Systemic and regional ischemia may trigger a potent systemic inflammatory response, which in addition to the aforementioned myocardial dysfunction, causes severe cardiocirculatory instability in most PBDDs [9].

Circulatory shock is a consequence of the impairment of at least one of the three determinants of cardiac output (preload, contractility and afterload). The early institution of appropriate maintenance strategies is fundamental. Up to 20% of organs and a large number of PBDDs are lost because the clinical management is challenging [11, 12]. The use of bedside checklists to achieve cardiovascular, respiratory and endocrine-metabolic target physiology has been associated with an increase in transplanted

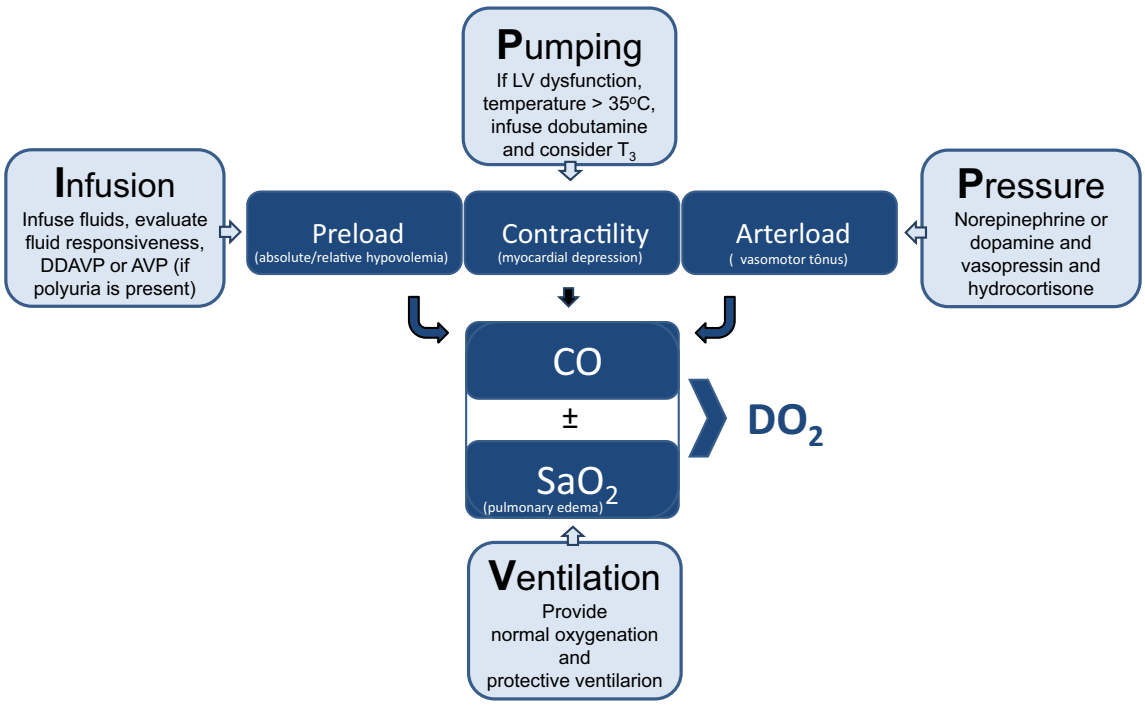

Fig. 3 Pathophysiology of haemodynamic instability after brain death and the adapted ventilation, infusion and pump/pressure (VIP) approach for clinical maintenance of potential brain-dead donors

organs [1, 3–5, 13, 14] and a decrease in PBDD losses due to cardiac arrest [15, 16].

A number of observational studies carried out in the USA tested the hypothesis that the use of a bedside checklist containing a standardized set of nine critical care end points, or donor management goals, could increase the number of organs donated per donor. Achieving seven of a predefined nine management goals may double the odds of obtaining four or more organs transplanted per donor [10–12].

The Ventilation, Infusion and Pumping/Pressure (VIP) approach (Fig. 3) is a simple mnemonic originally proposed to bring together key aspects of the management of shock states [13]. An adapted version of the VIP approach was proposed to simplify and to improve management standards of PBDD, providing a systematic sequence of procedures aimed at restoring DO_2 by adjusting mechanical ventilation, fluid and drug Infusions, and maintaining heart function (pumping/pressure) [14].

A bedside checklist based on the adapted VIP approach was implemented as a quality improvement intervention in 27 hospitals over 24 months. The adherence to the goal checklist was associated with a reduction of the odds of cardiac arrest episodes (the number of cardiac arrest episodes was inversely proportional to the number of treatment goals met), an increase in actual donors and in the number of organs recovered per donor [16].

The management of PBDD is a complex process that may be simplified by adopting clinical guidelines and alert tools to increase adherence to standards of care. Such organizational improvements require the intensive involvement of health team members in effectively applying care measures. In addition, they require interaction between the intensive care team, operating room professionals and transplant teams. However, the non-randomized design of available studies in this area limits the interpretation of results [11–13, 17]. A large cluster-randomized multicentre trial is now underway (NCT03179020) to evaluate whether a goal-driven checklist for the management of PBDD is useful in reducing cardiac arrest episodes and transplant organ shortages.

Strategies for optimization of donated organs

Intensivists managing donors should aim to increase organ availability and preserve long-term graft function. However, some organs develop dysfunction before management begins, and therefore incorrect decisions not to refer some PBDD on medical grounds are not infrequent occurrences in ICU [15].

Strategies to ensure adequate organ function must include continuous organ evaluation. This needs to happen before organ retrieval, during ex situ organ preservation, during reconditioning and before transplantation [16]. Timely decisions in ICU could eventually increase the deceased donor transplant rate in each country towards the benchmark figure of more than 70–100 transplants per million population [18].

Strategies of targeted timing for organ retrieval may be followed. It has been established that the number and quality of organs are not put at risk with a longer period of donor treatment, which may even be beneficial [19]. It is possible that hearts and lungs may not be utilized for transplantation after initial evaluation even though there is evidence that may function when donor treatment is prolonged for hours or days. The “relax and repair” approach [17] and an active “wait, treat and see” strategy [9] have been suggested to increase the number and quality of kidney and heart transplants. A median time of around 48 h from autonomic storm to cardiac function recovery has been proven by serial echocardiographic monitoring (Fig. 4) [9]. Left ventricular systolic dysfunction (LVSD) accounts for a number of non-acceptance of potential donor hearts; Madan et al. reported recently that hearts with transient LVSD can be successfully resuscitated and transplanted without an increase in recipient mortality [20]. Similar increases in the number and quality of transplantable organs may also be expected for lungs [21] and abdominal organs [17]. In addition, the time from brain death diagnosis and procurement outside a range between 12 and 30 h seems to be associated with a reduced incidence of cardiac arrest [19].

Multidisciplinary briefings and complete clinical information exchange with surgeons and other specialists should always take place. This is in an attempt to target donor care optimization including specific organ evaluation and functional monitoring. Competing interests of some organ-specific interventions (i.e. fluid administration, vasopressors, mechanical ventilation settings etc.) do not impede specific strategies for graft protection. These attenuate irreversible harm to grafts (including immune-mediated rejection), thus optimizing the care of recoverable organs. Intervening before organ retrieval in risky and unstable PBDD can mitigate organ injury, whereas therapies in the recipients have minimal effects on recovery from organ injury [22].

Evidence exists that meeting PBDD goals prior to organ recovery, even in expanded criteria donors, increases the number of transplantable organs, particularly lung and heart [11]. It is also evident that these goals require high-quality intensive care, specific education, proper experience and commitment, as well as time for treatment. In fact, goal achievement seems to be facilitated by more than 18 h of treatment from donor referral to organ retrieval, enhancing both quality and duration of intensive donor treatment [23–25].

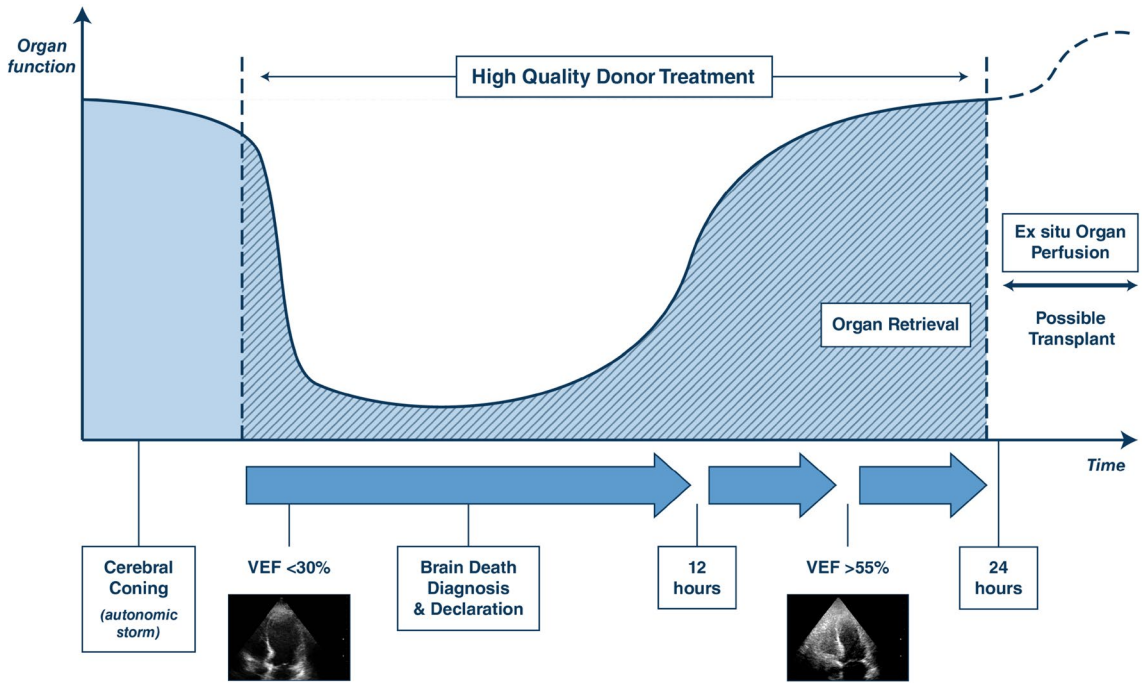

Fig. 4 Time-related organ function recovery after brain death. Rationale for prolonging high-quality intensive donor treatment

Kidneys are more resilient than other organs to acute insults occurring before and after brain death. It has been shown that cortical but not tubular necrosis may be the real irreversible obstacle to recovery. Acute kidney injury (AKI) with tubular necrosis is not an absolute reason to discard organs [17]. Ex situ perfusion including metabolic and biologic monitoring may be an effective bridge before transplant in extended criteria DBD.

Optimization of donated organs is also supported by indirect results of prospective trials: in the "mild hypothermia" study [23] decrease in kidney delayed graft function was associated with an extended median duration of treatment of more than 17 h; in the randomized trial proving that low dose dopamine infusion improves graft survival, the post hoc analyses after extended follow-up revealed that maximal efficacy depended on a prolonged infusion. That was probably a surrogate for a more stable haemodynamic state and quality donor intensive treatment [24].

In new ex situ machine perfusion techniques, it is important to underline that intensive care of potential organ donors is the first and most essential step in organ treatment aimed at preventing graft failure in the recipient; without high-quality intensive care and professional commitment all the traditional and the new advanced technologies of organ preservation and reconditioning cannot be effective in bridging towards successful transplantation. Quality in ICU management is also a prerequisite for avoiding the shift from DBD to donation after circulatory death (DCD) donation in the ICU and preserving the higher median number of organs recovered from heart beating donors [25] (and also potential for a shift in the other direction, i.e. from DCD to DBD as shown by Manara et al. [26]). Adherence to guidelines should be systematically audited in ICU. Quality indicators and quality assessment [27] should be used. It should be taken into consideration that only deeper insight into the pathophysiological background can offer room for improvement in donor treatment.

Key role of the intensivist in the organ donation process

There is a wide range of ICU mortality depending on patient and unit characteristics. Of those who die, between 8% and 13% are diagnosed as brain-dead [28]. However, the proportion of patients with brain injury who progress to neurologic death has decreased over time, especially among those with head trauma [29]. The process of diagnosing brain death, breaking bad

news to the family and medical management of PBDD requires intensivists to be broadly skilled. Intensivists must ensure that the diagnosis of death is accurately made, that the organs are transplanted in the best possible condition and that family members and ICU staff are supported through the donation process.

Communication is key [30]. This requires training and should be planned and carried out in a stepwise fashion. Information regarding the devastating nature of the initial insult should be communicated first, followed by a conversation about brainstem testing, and subsequently by confirmation of death. Time should be allowed to elapse between steps. The discussion of possible organ donation should be 'decoupled' from the proceeding discussions [31]. It is imperative that family members understand and accept that their loved one has died before it is appropriate to explore the option of organ donation.

There is now more than 50 years of experience in making the diagnosis of brain death with 100% specificity. Although there is no doubt about the clinical determination of brain death, diagnosing brain death is not always straightforward and appropriate training and experience are required [32]. Considering that there is no room for error or misdiagnosis, the determination of brain death should be preceded by the fulfilment of clinical prerequisites and performed by experienced and specifically trained physicians. Although the criteria for brain death are universal, the methodology for determining these criteria varies around the world, with the aid of local legal guidelines and in accordance with local legal processes. However, depending on the country, guidelines may not exist for the determination of death by neurological criteria. The absence of international standards for the determination of brain death has led to requests for the World Health Organization (WHO) to address these gaps. In response to these requests, the first phase of an international effort to develop an international guideline for the determination of brain death was completed in collaboration with the WHO [33].

Once death has been diagnosed, there is a shift in focus towards ensuring that optimizing organ function for transplantation fulfils the donor's wishes. This requires a thorough understanding of the pathophysiology of brain death and the physiological requirements of each organ. PBDDs require the same meticulous treatment performed by intensivists, anaesthesiologists, surgeons and nursing staff as living patients but with a focus towards saving other patients' lives [34].

Medical management of the PBDD differs depending on the organ(s) to be procured and transplanted. Excellent communication between the ICU, operating room team and the procurement organization is necessary to ensure organ optimization. For example, fluid management may vary depending on whether the lungs are to be transplanted or the period of medical management may be extended depending on the likelihood of myocardial recovery [35].

The process of organ donation can be physically and emotionally draining on ICU and theatre staff. Each episode brings with it new experiences and learning points. A debriefing session can be very useful for taking stock after each donation episode and for supporting staff members [36].

Research to improve organ donation: lessons learned from previous experiences

Despite the WHO's call for a major international effort to increase the supply of organs through education and research, very few randomized clinical trials have been published in this field of medicine. Ethical, infrastructure and operational issues, such as the follow-up of organs that allow correlation of donor interventions with outcome in the recipient, are undoubtedly great challenges for research [37].

Facing these challenges and developing clinical trials in this field can help in the understanding of fundamental aspects such as the inflammatory response related to brain death [38]. Compared to historical controls, donor management with increased attention to fluid resuscitation has been shown to reduce cardiovascular collapse and increase the number of organs transplanted per donor [39]. However, excessive fluid may also cause organ oedema. Optimal management of donor haemodynamics aims to achieve euvolemia, maintain blood pressure, and attain a cardiac output to achieve gradients of perfusion pressure and blood flow that promote organ function with minimal use of vasoactive drug support. One method to assess fluid optimization is to examine the pulse pressure variation (PPV) [40]. There is an association between increased PPV, indicating fluid responsiveness, and increased levels of inflammatory mediators such as IL-6 in the donor [32]. Accordingly, the Monitoring Organ Donors to Improve Transplantation Results (MOnIToR) Study was a large multicentre trial conducted to determine if protocolized fluid therapy would increase organs transplanted, reduce plasma IL-6 and improve survival in the recipients compared to usual care. Unfortunately, there was no reported difference between protocolized fluid therapy (targeting cardiac index, mean arterial pressure and PPV) compared to usual care in terms of number of organs transplanted and recipient mortality. On the other hand, the analysis of volume-responsive donors suggests that efforts to improve donor haemodynamics are likely worthwhile, as these subjects nearly

Table 2 Key points for the management of donation after brain death (DBD) in the ICU

The success of any donation process requires that PBDDs are detected and referred early
The adoption of checklists may improve the process of donation after brain death
Early institution of appropriate maintenance strategies is fundamental to increase the number and quality of organs for transplantation
Proactive interaction among intensive care team, operating room professionals and transplant coordinators is essential for the proper PBDD management
The intensivist plays a key role in the organ donation process
There is a great scarcity of clinical trials related to organ donation. It is necessary to leverage clinical trials to better understand the possibilities of improvement in the donation process

achieved a significant improvement in the number of organs used.

Future studies will need to demonstrate the benefit of protocolized fluid therapy strategies. It will need to be determined whether single interventions, such as protocol-guided fluids, may be sufficient to achieve desirable effect sizes; and finally, the correct development of translational research taking into account the inflammatory response to determine recipients' mid- and long-term survival [41]. Other biomarkers such as secretory leukocyte protease inhibitor (SLPI), a small protein synthesized by epithelial and inflammatory cells [42], might also be relevant predictors or drug targets [43] and should be further studied. This leaves open the possibility that interventions aimed at inflammation in the donor could be effective in improving organ transplantability.

Conclusion

The organ donation process has been improved over the last two decades with the involvement and commitment of many healthcare professionals. Clinical protocols have been developed and implemented to better organize the multidisciplinary approach to organ donation (Table 2). There is a shortage of research conducted in this subset of patients, which despite its challenges, must be encouraged to better understand the physiopathology and to optimize organ utilization.

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Compliance with ethical standards

Conflicts of interest
No COIs to declare by any of the authors of the manuscript.

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References

1. Niemann CU, Matthay MA, Ware LB (2018) The continued need for clinical trials in deceased organ donor management. Transplantation. https://doi.org/10.1097/TP.0000000000002512
2. Matesanz R, Domínguez-Gil B, Coll E et al (2017) How Spain reached 40 deceased organ donors per million population. Am J Transpl 17:1447–1454. https://doi.org/10.1111/ajt.14104
3. Saidi RF, Hejazii Kenari SK (2014) Challenges of organ shortage for transplantation: solutions and opportunities. Int J organ Transpl Med 5:87–96
4. Westphal GA, Slaviero TA, Montemezzo A et al (2016) The effect of brain death protocol duration on potential donor losses due to cardiac arrest. Clin Transpl 30:1411–1416. https://doi.org/10.1111/ctr.12830
5. Hoste P, Ferdinande P, Vogelaers D et al (2018) Adherence to guidelines for the management of donors after brain death. J Crit Care 49:56–63. https://doi.org/10.1016/j.jcrc.2018.10.016
6. Westphal GA, Coll E, de Souza RL et al (2016) Positive impact of a clinical goal-directed protocol on reducing cardiac arrests during potential brain-dead donor maintenance. Crit Care 20:323. https://doi.org/10.1186/s13054-016-1484-1
7. Jawoniyi O, Gormley K, McGleenan E, Noble HR (2018) Organ donation and transplantation: awareness and roles of healthcare professionals—a systematic literature review. J Clin Nurs 27:e726–e738. https://doi.org/10.1111/jocn.14154
8. Marchand AJ, Seguin P, Malledant Y et al (2016) Revised CT angiography venous score with consideration of infratentorial circulation value for diagnosing brain death. Ann Intensive Care 6:88. https://doi.org/10.1186/s13613-016-0188-7
9. Casartelli M, Bombardini T, Simion D et al (2012) Wait, treat and see: echocardiographic monitoring of brain-dead potential donors with stunned heart. Cardiovasc Ultrasound 10:25. https://doi.org/10.1186/1476-7120-10-25
10. Malinoski DJ, Patel MS, Daly MC et al (2012) The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. Crit Care Med 40:2773–2780. https://doi.org/10.1097/CCM.0b013e31825b252a
11. Patel MS, Zatarain J, De La Cruz S et al (2014) The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: a prospective study from the UNOS region 5 donor management goals workgroup. JAMA Surg 149:969–975. https://doi.org/10.1001/jamasurg.2014.967
12. Patel MS, De La Cruz S, Sally MB et al (2017) Active donor management during the hospital phase of care is associated with more organs transplanted per donor. J Am Coll Surg 225:525–531. https://doi.org/10.1016/j.jamcollsurg.2017.06.014

13. Weil MH, Shubin H (1969) The "VIP" approach to the bedside management of shock. JAMA 207:337–340
14. Westphal GA (2016) A simple bedside approach to therapeutic goals achievement during the management of deceased organ donors—an adapted version of the "VIP" approach. Clin Transpl 30:138–144. https://doi.org/10.1111/ctr.12667
15. Matesanz R, Domínguez-Gil B, Marazuela R et al (2012) Benchmarking in organ donation after brain death in Spain. Lancet 380:649–650. https://doi.org/10.1016/S0140-6736(12)61371-3
16. Hunter JP, Ploeg RJ (2016) An exciting new era in donor organ preservation and transplantation: assess, condition, and repair! Transplantation 100:1801–1802. https://doi.org/10.1097/TP.0000000000001300
17. Boffa C, Curnow E, Martin K et al (2017) The impact of duration of brain death on outcomes in abdominal organ transplantation. Transplantation 101:S1. https://doi.org/10.1097/01.tp.0000524966.72734.fb
18. Tullius SG, Rabb H (2018) Improving the supply and quality of deceased-donor organs for transplantation. N Engl J Med 378:1920–1929. https://doi.org/10.1056/NEJMra1507080
19. Inaba K, Branco BC, Lam L et al (2010) Organ donation and time to procurement: late is not too late. J Trauma 68:1362–1366. https://doi.org/10.1097/TA.0b013e3181db30d3
20. Madan S, Saeed O, Vlismas P et al (2017) Outcomes after transplantation of donor hearts with improving left ventricular systolic dysfunction. J Am Coll Cardiol 70:1248–1258. https://doi.org/10.1016/j.jacc.2017.07.728
21. Wauters S, Verleden GM, Belmans A et al (2011) Donor cause of brain death and related time intervals: does it affect outcome after lung transplantation? Eur J Cardiothorac Surg 39:e68–76. https://doi.org/10.1016/j.ejcts.2010.11.049
22. Giwa S, Lewis JK, Alvarez L et al (2017) The promise of organ and tissue preservation to transform medicine. Nat Biotechnol 35:530–542. https://doi.org/10.1038/nbt.3889
23. Niemann CU, Feiner J, Swain S et al (2015) Therapeutic hypothermia in deceased organ donors and kidney-graft function. N Engl J Med 373:405–414. https://doi.org/10.1056/NEJMoa1501969
24. Feng S (2017) Optimizing graft survival by pretreatment of the donor. Clin J Am Soc Nephrol 12:388–390. https://doi.org/10.2215/CJN.00900117
25. Domínguez-Gil B, Murphy P, Procaccio F (2016) Ten changes that could improve organ donation in the intensive care unit. Intensive Care Med 42:264–267. https://doi.org/10.1007/s00134-015-3833-y
26. Manara AR, Thomas I, Harding R (2016) A case for stopping the early withdrawal of life sustaining therapies in patients with devastating brain injuries. J Intensive Care Soc 17:295–301. https://doi.org/10.1177/1751143716647980
27. Hoste P, Hoste E, Ferdinande P et al (2018) Development of key interventions and quality indicators for the management of an adult potential donor after brain death: a RAND modified Delphi approach. BMC Health Serv Res 18:580. https://doi.org/10.1186/s12913-018-3386-1
28. de la Rosa G, Domínguez-Gil B, Matesanz R et al (2012) Continuously evaluating performance in deceased donation: the Spanish quality assurance program. Am J Transpl 12:2507–2513. https://doi.org/10.1111/j.1600-6143.2012.04138.x
29. Kramer AH, Zygun DA, Doig CJ, Zuege DJ (2013) Incidence of neurologic death among patients with brain injury: a cohort study in a Canadian health region. CMAJ 185:E838–E845. https://doi.org/10.1503/cmaj.130271
30. Simpkin AL, Robertson LC, Barber VS, Young JD (2009) Modifiable factors influencing relatives' decision to offer organ donation: systematic review. BMJ 338:b991. https://doi.org/10.1136/bmj.b991
31. Vincent A, Logan L (2012) Consent for organ donation. BJA Br J Anaesth 108:i80–i87. https://doi.org/10.1093/bja/aer353
32. Murugan R, Venkataraman R, Wahed AS et al (2009) Preload responsiveness is associated with increased interleukin-6 and lower organ yield from brain-dead donors. Crit Care Med 37:2387–2393. https://doi.org/10.1097/CCM.0b013e3181a960d6
33. World Health Organization (2017) Clinical criteria for the determination of death, WHO technical expert consultation, WHO Headquarters, 22–23 September 2014. World Health Organization, Geneva. http://www.who.int/iris/handle/10665/254737
34. Drake M, Bernard A, Hessel E (2017) Brain death. Surg Clin North Am 97:1255–1273. https://doi.org/10.1016/j.suc.2017.07.001
35. Ventetuolo CE, Muratore CS (2014) Extracorporeal life support in critically ill adults. Am J Respir Crit Care Med 190:497–508. https://doi.org/10.1164/rccm.201404-0736CI
36. Meyer K, Bjørk IT (2008) Change of focus: from intensive care towards organ donation. Transpl Int 21:133–139. https://doi.org/10.1111/j.1432-2277.2007.00583.x
37. (2011) The Madrid resolution on organ donation and transplantation: national responsibility in meeting the needs of patients, guided by the WHO principles. Transplantation 91(Suppl 1):S29–S31. https://doi.org/10.1097/01.tp.0000399131.74618.a5
38. Ozdemir BA, Karthikesalingam A, Sinha S et al (2015) Research activity and the association with mortality. PLoS One 10:e0118253. https://doi.org/10.1371/journal.pone.0118253
39. Salim A, Velmahos GC, Brown C et al (2005) Aggressive organ donor management significantly increases the number of organs available for transplantation. J Trauma 58:991–994
40. Michard F, Boussat S, Chemla D et al (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138. https://doi.org/10.1164/ajrccm.162.1.9903035
41. Murugan R, Venkataraman R, Wahed AS et al (2008) Increased plasma interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation. Crit Care Med 36:1810–1816. https://doi.org/10.1097/CCM.0b013e318174d89f
42. Majchrzak-Gorecka M, Majewski P, Grygier B et al (2016) Secretory leukocyte protease inhibitor (SLPI), a multifunctional protein in the host defense response. Cytokine Growth Factor Rev 28:79–93. https://doi.org/10.1016/j.cytogfr.2015.12.001
43. Li S, Wang S, Murugan R et al (2018) Donor biomarkers as predictors of organ use and recipient survival after neurologically deceased donor organ transplantation. J Crit Care 48:42–47. https://doi.org/10.1016/j.jcrc.2018.08.013
44. Domínguez-Gil B, Delmonico FL, Shaheen FAM et al (2011) The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. Transpl Int 24:373–378. https://doi.org/10.1111/j.1432-2277.2011.01243.x