Management of Potential Organ Donor: Indian Society of Critical Care Medicine (ISCCM) - Position Statement


Purpose and scope of the statement:

The position statement for management of organ donors is prepared by the Indian Society of Critical Care Medicine (ISCCM) with an objective of providing the standard perspective for management of potential organ/tissue donors after brain death in adults only regardless of availability of technology. This document should be used as guidance only and does not a substitute for proper clinical decision-making in the particular circumstances of any case. The endorsement of ISCCM does not imply that the statements given in the document are applicable in all or in a particular case; however, they may provide guidance for the users thus utilizing maximum organs from brain dead patient. Thus care of potential brain dead organ donor is “caring for multiple recipients”

The grading of recommendations is as follows:
A – We recommend
B – We suggest

Quality of evidence is:
1 – High to moderate
2 – Moderate to Low

Points covered/Scope:-Table 1

- Definition of Potential organ donor
- Definition of brain death and importance of brain stem death
- Declaration of brain death and tests done for confirmation of brain death
- Legal aspects of organ donation in India
- Physiological changes in brain dead patient and complications
- Medical Management of potential organ donor
Introduction:

In India the deceased donor organ donation rate is only 0.8 per million [while USA at 25.6 per million, UK at 18.3 per million and Spain at 32 per million][1]

On the background of increasing organ demand[2], compared to the number of organs available for transplantation, the responsibility to care for potential donor increases. A multi-disciplinary team approach is necessary for successful organ donation. [3] The physiology of all the available organs in the donor should be normalized and maintained till the time of organ retrieval. Often older people and marginal donors are also potential donor candidates, such cases need to be managed carefully, in order to improve the conversion rate and graft survival after donation. [2] Intensivist plays a vital role in identification, declaration of brain death and providing medical care to potential organ donors thereby improving rates of graft survival i.e. quality of organ donation. [3, 4, 5],

Indian Society of Critical Care Medicine (ISCCM) has recently released guidelines for end-of-life and palliative care in Indian intensive care units. [6] However, currently there are no guidelines for the identification of potential donor and management of identified potential organ donor in India.

1. **Potential organ donor:**

A potential organ donor is defined by the presence of either brain death or a catastrophic injury to the brain which could progress beyond reversibility and may fulfill brain death criteria.[7]

1.2 Mile-stones

Historically death was defined by the presence of putrefaction or decapitation, failure to respond to painful stimuli, or the apparent loss of observable cardio respiratory action. But with development in resuscitation measures and invention of mechanical ventilators, respiratory arrest was prevented. Vital functions can now be maintained artificially after the brain has ceased to function. Increasing incidence of medico legal cases necessitated definition of brain death.[8, 9, 10]

In 1959 Mollaret and Goulon coined the term on brain death “le coma dépasse”
In 1968, an ad hoc committee at Harvard Medical School reexamined the definition of brain death.

**Uniform determination of death Act** (UDDA): gave statutory recognition to the concept of brain death and equated this concept with traditional cardiorespiratory death. The fundamental tenet of this criterion is based upon a “cessation of the integrative functioning of the organism as whole” An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead.

1976 Conference of Medical Royal colleges. Published the statement on diagnosis of brain death. Clinical diagnostic testing for brain death became more refined.

1981 the U.S. President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research Published guidelines regarding brain death. The guidelines recommended the use of supplementary diagnostic tests to augment the clinical examination in brain death.

India follows U.K code. In India, the legal framework for organ donation is in place. According to the Transplantation of Human Organ Act (THOA-1994) legislation, deceased donation is a legal option. (THOA 1994)\textsuperscript{11, 12}

The Central Government has established a National Human Organs and Tissues Removal & Storage Network named NOTTO, which stands for National Organ and Tissue Transplant Organization. NOTTO has five Regional Networks ROTTO (Regional Organ & Tissue Transplant Organization) and each Region of the country will develop SOTTO (State Organ and Tissue Transplant Organization) in every State/ UT. This was based on the Transplantation of Human Organs and Tissues Rules, 2014.

Each hospital of the country related to transplant activity, either as retrieval or transplant center or both, has to link with NOTTO, through ROTTO/SOTTO as a part of National Networking.

1.3 What does brain death mean?

The Transplantation of Human Organs Act, 1994 (Central Act 42 of 1994),\textsuperscript{11} - definition of death:
'Deceased person' means a person in whom permanent disappearance of all evidence of life occurs,

1. By reason of brain-stem death or
2. In a cardio-pulmonary sense at any time after live birth has taken place.

'Brain-stem death' means the stage at which all functions of the brain stem have permanently and irreversibly ceased. However, cause of irreversible coma has to be established, preconditions met, and confounding factors are to be ruled out. [7, 8, 9, 10, 13]

[Ref figure 1 Components of definition of brain death]

Brain death is commonly caused by [8, 9, 10]

- Spontaneous intracranial hemorrhage
- Head injury due to motor vehicle accidents, recreational and industrial accidents, gunshot assault etc.
- Cerebral anoxia/ischemic injury (cardiac arrest due to asthma, asphyxiation, drug overdose, hanging, drowning, meningitis, carbon monoxide poisoning or primary cardiac arrest)
- Primary cerebral tumor.

1.4 How does brain death occur [8, 9]
In response to increased intracranial volume caused by any of the following

- Brain swelling,
- Blood collections,
- Obstruction to CSF flow (hydrocephalus)

The intracranial pressure (ICP) rises. As, the skull is a closed box, blood flow to the brain falls due to rising ICP and finally stops.

The brain dies ⇒ Irreversible ⇒ Patient dies

The criteria involved in the diagnosis and declaration of brain-death include

- Irreversible coma,
- Absence of brain-stem reflexes, and
- Apnea

See Figure 1: Components of definition of brain death.

India follows the UK concept of brain-stem death and the Transplantation of Human Organs (THO) Act was passed by Indian parliament in 1994 which legalized the Brain-stem death. [11] In 1995, THO rules were laid down which describe brain-death certification procedure.

The state of Maharashtra has passed a resolution making it mandatory to declare and certify “brain-death”. The Government Resolution underlines the responsibilities of hospitals registered under THO Act 1994 that is, authorized transplant centers. As the large number of brain-death occurs in non-transplant hospitals, it makes for the appropriate authority (Director of Health Services) to register all hospitals in the state that have an operation theatre and ICU as Non-Transplant Organ Retrieval Centers (NTORCs). These hospitals are permitted to certify brain-death as per procedure and then conduct organ retrieval for therapeutic purposes but not permitted to perform actual transplantation. Thus, it is mandatory now for all NTORCs and authorized transplant centers in the State to certify and notify the brain-death cases to Zonal Transplantation Co-ordination committee. This is a strong step to streamline the procedure for cadaveric organ retrieval and transplantation. [9]

The readers are advised to refer to the amendments and adoptions made to the act by their respective states in regards to the structure of the Deceased donor organ donation process.

1.5 Determination of brain death/Tests to be done for diagnosis of brain stem death
Clinical examination is important for determination of brain stem death.

1.5.1: **History taking and Physical examination findings that provide a clear etiology of brain dysfunction should be done, including review of CT/MRI films**

The determination of brain death requires the identification of the proximate cause and irreversibility of coma. **The evaluation of a potentially irreversible coma should be established with appropriate clinical or neuro-imaging evidences.**

1.5.2: **Exclusion of confounding factors that interfere in clinical diagnosis of brain death are:** [See Table 2]

a. Shock/ hypotension- Aim to have systolic BP≥ 90- 100mmHg with Vasopressors, if required
b. Hypothermia -temperature < 32°C (Core Temperature): Aim for core temperature between 32- 36°C. (32° for brain death declaration, 36° for carrying out apnea test)

c. Drugs known to alter neurologic, neuromuscular function and electroencephalographic testing, like anesthetic agents, neuro-paralytic drugs, methaqualone, barbiturates, benzodiazepines, high dose bretylium, amitriptyline, trichloroethylene and alcohols.

Review medication and ICU observation chart for drugs given, can wait for at-least 5 half-lives with normal renal and liver function to exclude a drug effect. Use Peripheral nerve stimulator for Train of Four Response (TOF) to rule out muscle relaxant effect. This is particularly important where patients are referred from periphery to tertiary care center

d. Brain stem encephalitis. Review history and Imaging

e. Guillain- Barre’ syndrome. Review history and Imaging

f. Encephalopathy associated with hepatic failure, uremia and hyperosmolar coma. Review history and Imaging

g. Severe hypophosphatemia. Check phosphate levels if in doubt

h. Neurotoxic snake envenomation- Review history.

<table>
<thead>
<tr>
<th>Table 2: Confounding factors that interfere in clinical diagnosis of brain death are:</th>
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<tbody>
<tr>
<td>1. Shock/ hypotension</td>
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<td>8. Drugs known to alter neurologic, neuromuscular function and electroencephalographic testing, like anesthetic agents, neuro-paralytic drugs.</td>
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1.5.3: Performance of a complete neurological examination. [refer figure 2]

I. Examination of the patient- for the response to noxious stimuli, administered through a cranial nerve path way. Spinal reflexes may be present. Suggested
sites for noxious stimuli are supraorbital groove bilaterally and Trapezius squeeze bilaterally

II. Absent pupillary reflex to direct and consensual light [cranial nerve II and III]; pupils need not be equal or dilated. Conditions interfering in the pupillary reflex are orbital trauma, head injury, cataracts, and medications like high dose dopamine, glutethamide, scopolamine, atropine, bretyllium or monoamine oxidase inhibitors.[figure 2b]

III. Absent corneal reflex [cranial nerve V and VII], oculocephalic (also called Doll eye movement), cough and gag reflexes [cranial nerve IX and X]. The corneal reflex may be altered as a result of facial weakness.[fig 2b]

IV. Cold Caloric test /Absent oculovestibular reflex [cranial nerve VIII, III and VI]: The external auditory canal should be clear of cerumen and tympanic membranes should be intact. Elevate the patient’s head by 30°. Twenty to fifty (20 to 50) ml of ice water irrigated into external auditory canal and over the tympanic membrane using a soft irrigation cannula. One should look for eye ball movement for which upper eyelids need to be retracted. Allow 1 minute response time after injection/irrigation of fluid and at least 5 minutes between testing on each side. No eye ball movements will be seen in brain dead patient.

Labyrinthine injury or disease, anticholinergics, anticonvulsants, tricyclic antidepressants, and some sedatives may alter response. [figure 2b]

1.5.4: Absent respiratory efforts in the presence of hypercarbia: Apnea test

I. The following pre-requisites must be met before carrying the apnea test\textsuperscript{[13,15]}

- Core temperature $\geq 36.5^\circ$C or 97.7°F
- Euvolemia or positive fluid balance in the previous 6 hours
- Normal PCO$_2$ or arterial PCO$_2 \geq 40$ mm Hg
- Normal PO$_2$. Pre-oxygenation for 15min with 100% Oxygen before carrying the apnea test, try to achieve an arterial PO$_2 \geq 200$ mm Hg for safely conducting the test

II: Steps for Apnea test (figure 2b, c)
Pre Oxygenate patient with 100% O₂ for ten to fifteen minute (to ensure denitrogenation of lungs) and do a base line ABG

- Connect a pulse oximetry and disconnect the ventilator.
- Deliver, 4- 6 l/min of O₂, via endotracheal tube into the trachea using a soft catheter.
- Look closely for any respiratory movements (abdominal or chest excursions that produce adequate tidal volumes).
- Measure arterial PO₂, PCO₂, and pH after approximately 8 – 10minutes later. (For every minute of apnea PaCO₂ rises by approximately 3 mm Hg).
- If respiratory movements are observed, the apnea test result is negative (i.e. it does not support the clinical diagnosis of brain death).
- Connect the ventilator, if during testing
  - the systolic blood pressure becomes < 90 mm Hg (or below age appropriate thresholds in children less than 18 years of age)
  - or the pulse oximetry indicates significant oxygen desaturation,
  - or cardiac arrhythmias develop;

III: Interpretation

- If respiratory movements are absent and arterial PCO₂ is ≥ 60 mm Hg  
  *(option: 20 mm Hg increase in PCO₂ over a baseline normal PCO₂), the apnea test result is positive (i.e. it supports the diagnosis of brain death).*[^13,15]

- If PCO₂ is < 60 mm Hg and PCO₂ increase is < 20 mm Hg over baseline, the result is indeterminate and a confirmatory test can be considered or apnea test repeated.
- When appropriate a 10 min. apnea test can be repeated after pre-oxygenation for 15 minutes with an FiO₂ of 1.0 and normalization of patients PaCO₂ to 40 mm Hg. [^13,15]

IV: Queries about Apnea test: [see Table 3]

<table>
<thead>
<tr>
<th>Table 3: Queries about Apnea test</th>
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<tbody>
<tr>
<td>a. When should the Apnea test done?</td>
</tr>
<tr>
<td>b. Who should do it?</td>
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<tr>
<td>c. Is consent necessary of Apnea test?</td>
</tr>
<tr>
<td>d. Trouble shooting for Apnea test</td>
</tr>
</tbody>
</table>
a) When should the Apnea test done?

Determination of brain death should be thorough and meticulous.

A formal evaluation of the brain stem reflexes is undertaken after above mentioned observation period. After the first clinical exam, the patient should be observed for a defined period of time for clinical manifestations that are consistent with the diagnosis of brain death. Most experts agree that a 6-hour observation period is sufficient and reasonable in adults and children over the age of 2 years.\(^\text{[1, 14, 15, 16]}\) (Grade 1A)

Pallis and Harley\(^\text{17}\) stress the importance of appropriate duration of observation that must be provided to ensure irreversibility of the pathological processes. Suggested observation period is included in table 4.

Table 4: Examples of observation periods in hours before testing for brain death:***\(^\text{(source Pallis C Harley DH. ABC of Brainstem death BMJ publishing group : 1996)}\)

<table>
<thead>
<tr>
<th>Apneic coma after</th>
<th></th>
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<tbody>
<tr>
<td>Major neurosurgery</td>
<td>&gt;4hr</td>
</tr>
<tr>
<td>Confirmed aneurysm</td>
<td></td>
</tr>
</tbody>
</table>

| Head injury (no secondary brain damage from hematoma, shock, or brain hypoxia) | >6hr |
| Spontaneous intracerebral bleed | >6hr |
| Brain hypoxia (drowning, cardiac arrest) | >24hr |
| Any of the above (with suspicion of drug intoxication but no screening facilities) | 50-100hr |
b) Is consent necessary for apnea test?

- Consent is not necessary for carrying Apnea test. (though an assent of family, informing them about the test been done, would be appreciated) (Grade 2B)

d) Troubleshooting during performance of Apnea test (Figure 3 & 4)

1. Patient’s systolic blood pressure (SBP) ≤100 mmHg: Vasopressors, inotropes and fluid boluses need to be administered to keep the blood pressure (BP) above the target. The apnoea test is aborted if systolic BP is ≤90 mmHg and the test needs to be repeated after stabilization. [1, 13, 15]

2. Oxygen saturation not maintained during apnea testing: The apnea testing is terminated if the saturation is ≤85% for more than 30 s. The test can be retried with T-piece and continuous positive airway pressure of 10 cm H₂O or more and oxygen flow of 12.0 L/min (Grade 2B). Reducing the positive end-expiratory pressure (PEEP) to 5 cm H₂O prior to disconnection from the ventilator for apnea testing can predict the tolerance to apnea. With the help of PEEP valve and one can give peep upto 25 cm H₂O (figure 4: PEEP valve)

3. Patient is hypothermic <35 °C: Guidelines for apnea testing are not valid and needs to be repeated after correction of hypothermia. [1]

4. Patient repeatedly desaturates or becomes hypotensive during apnea testing: One should consider ancillary tests for confirming brain death. Ancillary tests for confirming brain death such as EEG, cerebral angiography, transcranial Doppler and scintigraphy may be considered if available. These do not replace clinical assessment and it is notable that THOA in India does not mandate the use of ancillary tests. [13, 15] (See the section 1.7) (Grade 1A)

5. Baseline PaCO₂ ≥40 mmHg or ≤35 mmHg: A rise of ≥20 mmHg above baseline can be considered a positive apnea test in patients with elevated baseline PaCO₂. Reducing the frequency of ventilation to allow a PaCO₂ in the recommended range should be considered prior to testing of Apnea. [13, 15] (Grade 2B)
1.6: Observations which are compatible and incompatible with brain stem death

Compatible:
• Spinal reflexes
• Sweating, blushing, tachycardia
• Normotension without pharmacologic support
• Absence of diabetes insipidus

Incompatible:
• Decerebrate or decorticate posturing
• Extensor or flexor motor responses to painful stimuli
• Seizures
Reasons for spinal reflexes according to one hypothesis, the reflex movements represent hypoxia- and hypercapnia-induced activity of cervical cord neurons. Alternatively, they might be due to disinhibition of movement generators of the spinal cord. Another hypothesis is that mechanical compression/decompression of the spinal root or cervical spinal cord by neck flexion/extension can generate movement.\textsuperscript{[1,13]}

1.7: Ancillary tests
When the full clinical examination, including both assessments of brain stem reflexes and the apnoea test, is conclusively performed, \textbf{no additional testing is required to determine brain death (Grade 1A)}.\textsuperscript{[1,9,14]} Confirmatory tests like: electroencephalography (EEG) cerebral angiography, transcranial Doppler and radionuclide scan are not mandatory. \textbf{As per TOHA the ancillary tests are not mentioned at all, hence its legal acceptability is challenging.}\textsuperscript{[10,11]}

Indications for ancillary tests are:
1) Patients with cranial or cervical injuries, cardiovascular instability, \textsuperscript{[16]}
2) Severe facial trauma, otorrhagia, eye agenesis, \textsuperscript{[16]}
Which preclude the performance of a portion of the clinical examination,
3) reassure family members and medical staff. \textsuperscript{[14]}
4) Panel of doctors is in doubt or disagreement of the diagnosis \textsuperscript{[18]}

2.0 Legal aspects in India for Certification of brain death: [see Table 5]

<table>
<thead>
<tr>
<th>Table 5: Legal aspects for certification of brain death</th>
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<tbody>
<tr>
<td>Who can certify?</td>
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<tr>
<td>How many doctors required?</td>
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<tr>
<td>How many times test needed?</td>
</tr>
<tr>
<td>What is the observation interval between the second set</td>
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</table>

2.1: Who can certify & how many doctors required? \textsuperscript{[1, 11, 14, 18]}

Registered medical Practitioner with \textbf{appropriate authority} should do Apnea Test and can certify brain-stem death. \textsuperscript{[11]} \textbf{Diagnosis of brain death} is established and recorded by two doctors not belonging to the retrieval and transplantation teams
Out of the two doctors, one must be a specialist in neurology. The order of examination is irrelevant, i.e., it does not matter whether the neurologist performs the first or the second examination. \[16\]

**For certification of brainstem death** requires a panel four doctors.

1. Doctor in charge of the patient,
2. The doctor in charge of the hospital where the patient was treated,
3. An independent specialist of unspecified specialty (physicians, surgeons or intensivists) nominated from the panel of names approved by the appropriate authority,
4. Neurologist or neurosurgeon.

Form 10 should be filled and signed by the medical experts certifying brain stem death.

Amendments in the THO Act (2011) and THAO rules 2014 have allowed selection of a surgeon/physician and an anesthetist/intensivist, in the event of the non-availability of neurosurgeon/ neurologist.

2.2: **How many times the clinical examination and test are needed to be done and what is the interval between two tests?** \[11,14\]

Clinical examination and apnea test need to be done two times after an interval of six hrs. After the second test the team should start counseling the family regarding organ donation.

**The time of death is the end of second apnea test**

2.3: **What needs to be included in Medical record Documentation?** \[14\]

All phases of the determination of brain death should be clearly documented in the medical record:

- etiology and irreversibility of coma / unresponsiveness
- absence of motor response to pain
- absence of brainstem reflexes during two separate examinations separated by at least 6 hours
- absence of respiration with $pCO_2 \geq 60$ mm hg
• justification for, and result of, confirmatory tests if used

All the four doctors (members from Panel of The Board of Medical Experts) should sign tests done to document absence of brainstem function namely pupillary reflex, doll’s head eye movement, corneal reflex (both sides), gag reflex, cough (tracheal), eye movements on caloric testing bilaterally, absence of motor response in any cranial nerve distribution and apnoea test.[18]

In India, Form 10 is necessary for brain death certification.[11]

3.0 Communication platform:

The Medical expert registered with appropriate authority need to have a dialogue with the relatives about carrying of the tests for brain stem death. Given the situation and delicate sentiments of family/caregivers, the person responsible for breaking news to family/caregivers about patient’s brain-stem death, should be sensitive to the responses and feelings of the family members/caregivers.

The ICU physician should communicate the confirmation of brainstem death to transplant coordinator who in turn can communicate to family and make request for the organ donation (Grade 1A). Simultaneously, the administrators of the hospital should be communicated to stop the further billing once diagnosis of brainstem death is confirmed and family has consented for the organ donation.

3.1: The process of consent for organ and tissue donation involves: [10, 11, and 14]

1) the deceased
2) Next of kin
3) Coroners consent (medico legal cases)

1) The deceased:

The deceased wishes must be ascertained through hospital staff/relatives/donor coordinator (driving license etc. wherein the provision for donation may be incorporated after notification of THOA rules). In India even if the deceased wish are known, the next of kin need to formally consent and sign the consent form.[11]
The NOTTO Organ Donor Register is a computerized database which records the wishes of people who have pledged for organ and tissue donation and decided that, after their death, they want to leave a legacy of life for others. There are many hospitals and organizations those are also maintaining the list of persons who have pledged organ donation with them, all this will be a part of NOTTO website for National Register.

2) Next of kin consent

Hospital staff need to speak with the relatives about organ donation on behalf of deceased.

**The surrogate decision making authority**

1) Spouse

2) Son or daughter (18 years or over)

3) Parent.

In case of dispute in the family or difference of opinion in the family, ample amount of time should be given to the family to discuss, settle and give a final decision.

Form 8 need to be filled and signed to record the status of the cum consent by near relative or lawful possessor of brain-stem dead person.

It is necessary to inform police about organ donation consent to the Station House Officer or superintendent of Police or Deputy Inspector general, if it is a documented medico legal case. Once the consent for organ donation is achieved the cost for maintenance of cadaver or retrieval or transportation or preservation of organs or tissues their transportation and preservation may be borne by the recipient or institution or government or non-government organization but not by the donor family (Grade 1A).

3.2: Areas of controversy:

Data Protection and confidentiality of recipients has to be maintained. Donor’s family cannot have access to recipient’s name.

As mentioned earlier the police need to be informed about organ donation consent in case of medico legal cases. A copy of consent should also be sent to the designated post mortem doctor. It shall be ensured that by retrieving organs the determination of the cause of
death is not jeopardized. The medical report in respect of the organs or tissues retrieved prepared by retrieving doctors shall be taken on record in post mortem notes.

4.0: **Medical suitability for organ donation**:

The patient must be medically suitable to donate organs for transplantation. Criteria for suitability change over time and vary according to recipient circumstances. Early determination of the suitability for transplantation of specific organs facilitates the development of focused medical management strategies (e.g. more aggressive fluid therapy when lung donation is contraindicated).

4.1: **Exclusion criteria for organ donation**

1) Infection with human immunodeficiency virus, Human T cell leukemia-lymphoma virus, 2) Systemic viral infections (measles, rabies, adenovirus, parvovirus) and herpetic meningoencephalitis, 3) Active malignant disease or a history of malignancy that poses a high risk for transmission irrespective of the apparent disease-free period (e.g. melanoma, choriocarcinoma)

Bacteremia or fungemia are not absolute contraindication to donation. Acute organ dysfunction in particular acute renal failure in a potential donor with prior renal function, is not a contraindication to donation.

4.2: **What is the accepted age range for multiple organ and tissue donors?**

[See table: 6 Age limit for deceased organ donor]

There is no maximum age for donation; however, comorbidities that develop together with aging make donation less acceptable. Marginal or expanded criteria donors are those presenting clinical conditions that might reduce graft survival, impair its function or are at high risk of disease transmission. The use of marginal donors is only justified when the life expectancy after transplantation is higher compared with conventional clinical treatment.

**Recommendation**: For recipients under 45 years old, the ideal age of deceased donors is depicted in table 6
Older persons (e.g. up to 80 yrs. of age)\textsuperscript{[16]} (Grade 2B) and those with a history of hypertension and diabetes mellitus need to be worked up for individual organ function like albumin: creatinine ratio for kidney function.

Table 6: Age limit for deceased organ donor

<table>
<thead>
<tr>
<th>Deceased donor organs</th>
<th>Age limit</th>
<th>Grading of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>Up to 60 years old</td>
<td>Grade 2 B</td>
</tr>
<tr>
<td>Liver</td>
<td>Up to 60 years old</td>
<td></td>
</tr>
<tr>
<td>Kidney-pancreas</td>
<td>18-45 years old</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>7 days to 50 years old</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>45 years old</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>60-65 years old</td>
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</tbody>
</table>

5: Care of organ donor:

Intensive care specialist assists critically ill patient to recover from illness and lead a good quality of life. Brain stem death usually results in complex multiple organ failure. In such cases, the decision to stop or remove specific brain related intensive treatments needs to be taken. However, extra-cranial physiological support may be continued till the determination of brain death or very severe irreversible brain damage. Appropriate management of donor before and after brain death, may result in increasing the frequency and improving quality of donor organs.\textsuperscript{[3,7]}

All health care personnel and ICU attendants should have a responsible and professionally behavior at the bedside of the patient. Medical procedures and investigations should only be done if they are required to facilitate the donation procedure.

5.1: Physiological and metabolic changes during brain death:
5.1.1: Cardiovascular system:

Hemodynamic instability and cardiac dysfunctions are always encountered in patients after brain death. Myocardial dysfunction often occurs as a result of severe brain injury. The exacerbated stress response i.e. “sympathetic storm” —results in hypertension, tachycardia and arrhythmias. Though usually of short duration, it may lead to cardiac dysfunction, cardiac ischemia, myocardial and conduction system necrosis. Further spinal cord ischemia is followed by deactivation of sympathetic storm and loss of cardiac stimulation. This leads to vasodilatation and cardiac dysfunction, clinically presenting as hemodynamic instability in potential donor. Other factors contributing to hypotension are diuretics (mannitol), hyperglycemia-induced osmotic diuresis, diabetes insipidus, hypothermic “cold” diuresis, inadequate fluid resuscitation, and decreased oncotic pressure after crystalloid resuscitation, ongoing blood loss, rewarming of patient, relative adrenal insufficiency as result of trauma and critical illness.

5.1.2: Diabetes insipidus:
Diabetes insipidus is a common problem in brain dead patients. It occurs in about 80% of the patients with brain death. However, absence of diabetes insipidus does not mean that the patient is not brain dead. Diabetes insipidus results from deficiency of anti-diuretic hormone due to loss of posterior pituitary function\[^2\] leading to polyuria. In patients with urine output more than 200 ml/hour for consecutive two hours, diagnosis of diabetes insipidus should be suspected. If left untreated, diabetes insipidus often leads to hypovolemia and hypernatremia. Hypernatremia may adversely affect the outcomes for renal and liver transplants (Grade 2A). [22, 23,24,25].

**5.1.3: Hypothermia:**

Brain death results in hypothermia due to loss of thermoregulation, reduced metabolic rate, excessive heat loss and loss of protective mechanisms such as vasoconstriction or shivering. [3] Exposure and administration of cold fluids may further increase the risk of hypothermia. Hypothermia is best avoided or prevented rather than treated. Once hypothermia sets in, it is difficult to warm patients and it has direct effect on cardiac function, arrhythmias, coagulation cascade and oxygen delivery to tissues.

**5.1.4: Hormonal dysfunction:**

Circulating triiodothyronine (T3) may be low in patients with brain death. [26] Thyroid hormone deficiency along with cortisol deficiency, may contribute to hemodynamic instability. [27] The data also suggest that function of anterior pituitary is partially preserved, with normal levels of cortisol and thyroid hormone, or low thyroid hormone with normal/raised thyroid stimulating hormone (TSH) levels consistent with sick euthyroid syndrome. [28] Hyperglycemia is common in brainstem death patients because of reduced insulin concentrations and insulin resistance. [3]

**5.1.5: Anaemia, coagulopathy and immunological changes:**

Traumatic bleeding commonly results in anemia. Furthermore, coagulopathy and fluid administration may cause exacerbation of anemia. Significant rise in pro-inflammatory cytokines such as interleukin-6 (IL-6) has been observed in brain dead potential organ donors which could be one of the causes of coagulopathy. [28,29] The other possible causes include dilutional coagulopathy due to fluid administration, and it may be
worsened by hypothermia. [29]

6: **Multisystem management of multi-organ donor:**

6.1: **General Care** [30]
General measures of infection control should be applied. These include:

Hand Hygiene – as per standard medical/nursing care (Grade 1A)

Frequent turning of patient for decubitus ulcer prophylaxis, skin care, dressing changes, urinary and intravascular catheter care, must be meticulous to minimize the risk of infection. (Grade 1A)

Bronchial toilet – improves elimination of secretions and therefore improves chances of lung donation. (Grade 2B)

Eye care – care to ensure no corneal abrasions or ulcers and improves the chance of corneal donation. Reduce heat loss and actively warm if necessary to maintain core temperature 35˚C (Grade 1B)

A nasogastric tube must be inserted for gastric decompression and prevention of aspiration. (Grade 1B)

Arterial and central venous lines should be inserted preferably into the upper extremities, because femoral line readings can become inaccurate during surgical procedure for organ procurement. (Grade 2B)

6.2: **Monitoring** [30]

Monitoring is a crucial part of the medical management of potential organ donor. Routine monitoring includes ECG, blood pressure, pulse oximetry, core temperature, hourly urine output and central venous pressure (Grade 1A) Bedside echocardiography for assessment of fluid deficit.(Grade 1A) Use of a Swan-Ganz catheter/Cardiac Output monitors, should be reserved for unstable donors, who have persistent acidosis with evidence of tissue hypoperfusion. (Grade 2B)

6.3: **Laboratory** [30]
Arterial blood gas, lactate, electrolytes and blood sugar levels need to be monitored every 2-4hourly.\(^9\) (Grade 1A) Parameters like hemoglobin, hematocrit, complete blood count, blood glucose, urine analysis, blood urea nitrogen, serum creatinine, serum electrolytes, liver function tests, coagulation profile and microbiological screening for hepatitis B, C, hepatitis B core antigen, HIV, IgM and IgG for cytomegalovirus are necessary. (Grade 1A).

Mandatory investigations include Blood group, HIV Antibody, HBSAg, HCV antibody. (Grade 1A)
However, Risk of transmission of infection may still remain

Cultures of blood and urine may be required, if there is evidence of infection, or if the patient is hospitalized for more than 72 hours (Grade 2 B). Some additional tests may be required for multiorgan donors e.g. echocardiography for heart and bronchoscopy for lung transplantation.

**7: Goals for maintenance of potential organ donor**\(^{[3,30]}\) (Fig 6)

One should aim to maintain body temperature, ensure adequate oxygenation, circulating volume, cardiovascular stability, and adequate urine output

A simple method to maintain potential donor is ‘rule of 100’\(^{[1]}\) (Grade 1B) **Table 7**

<table>
<thead>
<tr>
<th>Table 7: ‘Rule of 100’</th>
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</thead>
<tbody>
<tr>
<td>Systolic arterial pressure &gt; 100 mm Hg,</td>
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<tr>
<td>Urine output &gt; 100 ml/h,</td>
</tr>
<tr>
<td>PaO2 &gt; 100 mm Hg,</td>
</tr>
<tr>
<td>Haemoglobin concentration &gt; 100 g/Litre (10gm/dl)</td>
</tr>
<tr>
<td>Blood sugar 100 mg/dl</td>
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</tbody>
</table>

**Figure 6: Goals for maintenance of potential donor**

The medical management of organ donor can be broadly divided into

- Management of hemodynamic
- Management of metabolic derangement
- Temperature management,
- Management of respiration and hematological parameters
- Nutrition management

The treatment aspects of these parameters are summarized below
7.1: Management of hemodynamic
Goals for management of hemodynamic status of the donor: -[7, 30]

1) To maintain normovolemia and blood pressure,
2) Optimize cardiac output so as to maintain perfusion pressure of all organs with the use of the least amount of vasoactive support.

7.1.1: Hypertension: Because of the transient nature of autonomic storm, antihypertensive are usually not required. If needed, short acting antihypertensive such as esmolol, sodium nitroprusside, hydralazine, labetalol, or nitroglycerine should be used. (Grade 1B). Antihypertensive is not required for long.

7.1.2: Hypovolemia:
Intravenous fluid administration is required for the management of hypovolemia. However, the decision for selection of fluid depends on serum electrolytes, sugar level, hemodynamic of the patient, estimated volume deficiency, polyuria from diabetes insipidus. Organs such as lungs may require minimal fluid for optimizing function.[31] The suitable organs for transplantation should be identified in advance to plan focused medical management of fluid replacement. Significant positive fluid balance is associated with progressive pulmonary dysfunction. [32]
One should check for signs of continuing haemorrhage (external, GI, urinary, abdominal, etc.) (Grade 1 A)
Discontinue medications that may contribute to hypotension (e.g. antihypertensive, beta-blockers) (Grade 1A)

Three management strategies are commonly adopted and treatment is escalated depending on the clinical response. These strategies are: [7]

A) Volume expansion
B) Vasopressors, Inotropes.
C) Hormonal replacement

A) Volume Expansion/Preload [7]

Which fluid?
- Crystalloids with balanced salt content so as to avoid hypernatremia (concurrent DI),
hyperchloraemic acidosis (increases renal vascular resistance, confounds base excess) when used as resuscitation target (Grade 1A). Administration of excessive intravenous fluids containing 5% dextrose may further complicate the hyperglycemia and hypothermia.\textsuperscript{[32,33,34]}

- **Avoid colloids.** Hydroxyethyl starches are contraindicated in organ donors because they can damage renal epithelial cells and cause early graft dysfunction in the transplanted kidneys.\textsuperscript{[7,35]} [Grade 1A]
- Albumin solutions (20%, 4%) may be considered to reduce the amount of volume given, although usually only moderately effective. (Grade 2 B). The high sodium content of albumin-based solutions needs to be taken into account
- The most commonly used fluids are Ringer’s lactate, Plasmalyte-A, Ringer’s acetate, half normal saline\textsuperscript{[1,7,33,34]} (Grade 1A)
- Packed red cells should be transfused to achieve a haematocrit of 30 percent in order to maintain oxygen delivery.\textsuperscript{[7]} (Grade 2A)

**Monitoring\textsuperscript{[7]}**

Central venous pressure measurement alone is a poor guide for directing resuscitation and alternative techniques can be used to assess effective fluid administration responsiveness (Grade 1A).
- Repeat bedside echocardiography. (Grade 2A)
- Pulse pressure variation is a method that has been used to determine optimal fluid status. (Grade 2 B)
- Urine output 1-3 ml/kg/hr (in the absence of polyuria due to diabetes insipidus or diuretics)(Grade 1A).
- Cardiac index >2.5 (note – high cardiac output state due to vasodilatory shock may be a confounder). (Grade 2 B)]
- Central venous oxygen saturation (ScvO2) >70% (note – low basal metabolism due to brain death may be a confounder) (Grade 2 B)].

**B)Vaspressors**
An adequate perfusion pressure should be maintained. The targets for systolic blood pressure and mean arterial pressure should be >100 mm Hg and ≥ 70 mmHg respectively (Grade 1A). [3]

Vasopressor medicines may be required frequently to support mean arterial pressure once hypovolaemia has been excluded/corrected. Vasopressin in pressor dose (1-2 U/hr.) plays an important role in stabilizing the hemodynamic of brain-dead patient. [36, 37] (Grade 1 A). Vasopressin up to 2.4 units/hour may reduce the requirement of other ionotropes. [3] The utility of low-dose vasopressin to treat diabetes insipidus, aid restoration of vascular tone, and reduce epinephrine requirement was first identified in brain-dead patients receiving long-term support. When the loss of vascular tone is preventing achievement of donor goals, low-dose vasopressin may allow reduction or elimination of catecholamine use, as in other ICU patients[1]. Canadian guidelines recommend vasopressin as the first-choice vasopressor for donor resuscitation. [36, 37]

Norepinephrine is also commonly used for this purpose. [34] (Grade 1A)]. Norepinephrine is required in higher doses compared to epinephrine. As far as possible, high doses of norepinephrine>0.05 mg/kg/min should be avoided. (Grade 2 B).

A study in brain dead patients has shown that pressor dose of vasopressin and epinephrine combination effectively increases the mean arterial blood pressure with increase in total peripheral resistance index and cardiac index. Dopamine can be used as well, but has an increased incidence of arrhythmias. [34] Intravenous fluids and Inotropes/vasopressors (dopamine, dobutamine, epinephrine, vasopressin, and norepinephrine) should be administered based on the central venous pressure and bed side 2Dechocardiography. [Recommendation (Grade 1 B)]

C) Hormonal replacement:
There are no clear recommendations regarding T3 administration for improving hemodynamic status and cardiac function in potential donors and also the results are not clear. [1, 7] Moreover, easy availability of T3 is not easily available in India. Thyroxine 300-400mcg through Nash-gastric route can be given in hemodynamic ally unstable patients, but absorption and clinical effect is not proven (Grade 2 B)

7.1.3: Arrhythmias:
Efforts should be made to prevent arrhythmia or promptly treat it, because of problems associated with them. It is more commonly seen in case of longer lag between brain death and organ removal.
Prevention of arrhythmia: Electrolytes, blood pressure, fluid volume and body temperature should be carefully monitored and maintaining within normal range to reduce the risk of development of cardiac arrhythmia. (Grade 1 A)

Treatment of tachyarrhythmia: If arrhythmia occurs, it can be treated with standard therapy such as Amiodarone or Cardioversion (Grade 1 B)

Atropine is not useful in management of bradycardia whereas adrenaline, isoprenaline or pacing may be effective(Grade 2 B).\textsuperscript{[38]}

7.2: Management of Hormonal and metabolic derangement:

7.2.1:Hormonal resuscitation:

Some studies have recommended its use in persistent hemodynamic instability and/or when ejection fraction is< 45% on echocardiography and when heart donation is planned.\textsuperscript{[7, 28, 39]} However, there is not strong evidence for use of hormonal resuscitation.\textsuperscript{[7, 28, 39]} There is limited data on the benefit of hormone administration in humans. Small studies with thyroid hormone have not shown benefit on hemodynamic status in brain-dead patients.\textsuperscript{[3, 7, 26, 40]}

Thus, the evidence on anterior pituitary or thyroid dysfunction in brain death is conflicting. In patients in whom lung transplant is distinct possibility, use of methylprednisolone has shown some benefit.\textsuperscript{[41]} The results of a retrospective analysis of 118 consecutive organ donors, of which 80 received high-dose methylprednisolone during donor management demonstrated improved oxygenation at organ recovery. With high dose steroid treatment, significant increase in the number of lungs utilization was seen possibly because of the anti-inflammatory benefits of steroid.\textsuperscript{[1]}

We suggest (Grade 1B):\textsuperscript{[3, 7, 34, and 38]}

a) Vasopressin 1 U bolus followed by an infusion of 0.5-4.0 U/h (desmopressin intranasal has a selective action on the V2 receptors and a half-life varying from 6 to 20 h.

b). Methylprednisolone: 15 mg/kg immediately after diagnosis of brain death and 24th hourly thereafter. Another option 250mg followed by 100mg/hour till the organ retrieval.

c. Insulin infusion to maintain blood glucose between 80 and 150 mg.

d. Thyroxin (T\textsubscript{4}) 20 mcg bolus followed by infusions of 10 mcg/h. Tri-iodothyronine (T\textsubscript{3}) given as a 4-mcgbolus followed by an infusion of 3 mcg/h. T4 improves
hemodynamic and prevents cardiovascular collapse in hemodynamic ally unstable organ donors. However, intravenous triiodothyronine is generally not available. So suggested thyroxine oral 300-400mcg/8 hourly instead of tridothyronine (NOTTO)

7.2.2: Diabetes insipidus (DI):
Desmopressin or vasopressin should be used early in the management of diabetes insipidus. The dose of desmopressin and vasopressin is given along with acceptable urine output in table 8.

Table 8: Dose of desmopressin and vasopressin with acceptable urine output

<table>
<thead>
<tr>
<th>Acceptable urine output</th>
<th>30–200 mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
</tr>
<tr>
<td>Desmopressin</td>
<td>10 mcg/nasal puff; 1-2 nasal puffs every 4 hours</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>IV infusion at a dose of 0.5–2.0 U/h</td>
</tr>
</tbody>
</table>

Early use of antidiuretic agents in suspected diabetes insipidus may prevent physiological instability due to hypovolaemia and hypothermia. Large amount of fluid loss in the urine should be replaced by intravenous fluids using balance salt solution or fluids with low-sodium content (5% dextrose or 0.45% saline) to maintain sodium level between 135-145 mEq/l. (Grade 1A)

7.3: Metabolic derangement:
Intravenous fluids are also required to maintain normal fluid volume and electrolytes balance. Serum sodium and potassium should be monitored every 2–4 hours (Grade 1 B)]. Insulin infusion may be required for maintenance of normal blood glucose. Doses of insulin required for maintaining glucose control may be higher than normal. Maintain blood sugars 80–150mg/dl. [7] (Grade 1A)

7.4: Temperature, respiration and hematological management:
7.4.1: Temperature
Prevention of hypothermia is easier compared to its reversal. Active warming helps to
prevent hypothermia. Efforts should be made to maintain temperature $>35^\circ$C. $^{[3]}$ (Grade 1A). Surface warming should be done in all patients with hypothermia. The patients with body temperature of less than 34$^\circ$C should be given core warming. In such cases, inhaled gases should be warmed and humidified by using humidifier. (Grade 2B). Intravenous fluid should also be warmed if large volumes are to be administered (Grade 2B)

### 7.4.2: Respiration
Respiratory passage should be clear without any obstruction. In order to achieve this, routine measures such as suctioning, positioning and turning should be continued. A technique such as positive end-expiratory pressure helps to maintain oxygen delivery to the organs due to reduction in atelectasis. Interstitial fluid overload should be avoided. Oxygen saturations within normal limits and normocapnia should be maintained. (Grade 1A)

### 7.4.3: Hematological management
In case of active bleeding, the cause of bleeding should be corrected at the earliest. $^{[3]}$ Sometimes, transfusion of blood, coagulation factors and platelets may be needed to correct severe anemia and/or coagulopathy (Grade 1B). In case of worsening coagulopathy, organ removal should be expedited. $^{[34]}$ Transfusion of blood or blood products should be done only if necessary. (Grade 2B)

### 7.5: Infection management
Donor should be infection free. Routine use of antibiotic prophylaxis is not warranted (Grade 2B). Use of antibiotic agents on the basis of results of Gram’s staining of aspirated secretion and positive cultures.

### 7.6: Management of nutrition
Nutrition should be continued as per standard ICU protocol (Grade 1B). Nutrition should be continued in patients awaiting consent for organ donation from the caregivers. Continuing enteral feeding in the potential donors may help in providing beneficial effects for organ functioning. $^{[42, 43]}$

### 8. Medicines to be avoided (Grade 1A)
Drugs may cause adverse events related to different organs. Patient related and drug related
factors may be responsible for the toxic effects of induced by medicines.\textsuperscript{[44]} Drug related factors responsible for organ damage include drug’s pharmacology, mechanism of action, dose, frequency of administration, duration, form of administration, drug interaction potential etc. Medicines causing liver or kidney toxicity are listed in table 9.

The following checklist may be used for management of potential organ donors.

\section*{9.Summary:}

Brain stem death is usually followed by an expected pattern of complex multiple organ failure, hence an appropriate support to the donor before and after brain death, can increase the number and quality of donor organs. The medical management of organ donor can be broadly divided into cardiovascular management, hormonal or management of metabolic derangement, management of temperature, respiration, hematological parameter and nutritional support. Early identification of organs for donation helps to optimize the medical strategies. The guidance provided in this statement does not substitute proper clinical decision-making in particular case, but will help intensivist for the management of brain death for organ and tissue donation. (Check list for management of potential organ donor Table:10)

\textbf{Table 10: Check list for the management of potential organ donors:}
<table>
<thead>
<tr>
<th>Basic monitoring</th>
<th>Routine investigations</th>
<th>Special management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Investigation</td>
<td>Management</td>
</tr>
<tr>
<td>Continuous monitoring of core temperature</td>
<td>Body temperature &gt;35°C</td>
<td>Peripheral warming (and core warming, if required)</td>
</tr>
<tr>
<td>Urine output</td>
<td>Urinary output, ≥1.0 ml/kg/hr</td>
<td>Left ventricular ejection fraction ≥45%</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>&gt;95 percent</td>
<td>Mean arterial pressure ≥60 mm Hg</td>
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</tbody>
</table>
Table 9: Common medicines causing liver and kidney related adverse events

<table>
<thead>
<tr>
<th>Hepatotoxic medicines[^43]</th>
<th>Nephrotoxic drugs[^44]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Full dose ritonavir</td>
<td>Radiocontrast media</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Quinine</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Hydralazine</td>
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<tr>
<td>Stavudine</td>
<td>Lovastatin</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Sustained release niacin</td>
<td>Barbiturate</td>
</tr>
<tr>
<td>Halothane</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Isoflurane, Enflurane, Desflurane</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Gold salts</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Azathiaprine</td>
<td>Metyhysergide</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Gold salts</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Penicillamine</td>
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<tr>
<td>Felbamate</td>
<td>Captopril</td>
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<td>Phenytoin</td>
<td>Mercury</td>
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<td>Chlorpromazine</td>
<td>Acetaminophen</td>
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<tr>
<td>Haloperidol</td>
<td>Indinavir</td>
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<tr>
<td>Risperidone</td>
<td>Lithium</td>
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<td>Quetiapine</td>
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<td>Olanzapine</td>
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<td>Clozapine</td>
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<td>MAO inhibitors</td>
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<tr>
<td>Tacrine</td>
<td></td>
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<tr>
<td>Methyldopa</td>
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</table>
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