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1. DONOR AND GRAFT

1.1. Organ allocation

French patients are placed on a waiting list at their local transplant centre under the supervision of the French National Transplantation Agency (Agence de la Biomedecine). Allocation of grafts follows geographical criteria (graft proposed first at the local level, then regional, then national). When they are several centers in the same geographical area, there is a turn between them. Patients with isolated respiratory failure may benefit from the high emergency lung transplantation (HELT) allocation system if they meet prioritization criteria of severity (1).

Cystic fibrosis	**Pulmonary fibrosis**	**Pulmonary hypertension**
Invasive MV or ECMO or	Invasive MV or ECMO or	Invasive MV or ECMO or
$PaCO_2$ > 80 mmHg and NIV>18 h/24 for 72 h	SaO_2 < 90% despite high concentration O_2 therapy and medical maximal treatment	NYHA IV and cardiac index <2L/min and PVR>1200 dyn.s.cm^{-5} Maximal medical treatment for 72 h

1.2. Donor

Two modalities of organ donation exist for lung transplant: brain death donor, and donation after cardiac arrest following treatment withdrawal (also called Maastricht III). The sequence to achieve transplantation once the agreement to perform organ donation follows different steps:
- in case of brain death donor, timing for patient entering in the OR is determined by the thoracic surgeon, depending on the graft extraction logistic, and dissection difficulty expectation of the recipient;
- in case of donation after circulatory death (Maastricht III), an normothermic regional perfusion (NRP) is implanted in the ICU after cardiac arrest if donation concern more organs than lungs. If only lungs are extracted, the NRP is not implanted, and the donor is transferred immediately to the OR. All lungs graft undergoes ex-vivo reconditioning for at least two hours before implantation into the recipient.

1.3. Ex-Vivo Reconditioning

The ex vivo lung perfusion (EVLP) is issue from the Toronto group(2) and locally adapted(3).
Inside the X-VIVO chamber (X-VIVO Perfusion), the pulmonary artery and the funnel-shaped cannula sewn to the left atrium are first connected to achieve a closed-system associated with ECMO. During the gradual increase in temperature, and before the initiation of ventilation, a bronchoscopy with broncho-alveolar lavage was performed to clear out secretions. When 31°c was reached, ventilation was started with 3 ml.kg^{-1} of donor ideal body weight with a positive end expiratory pressure (PEEP) 5 mmHg and FiO_2 21%. Then tidal ventilation is increased to obtain 7 ml.kg^{-1} at 37°C. At the same time, the perfusate output of Steen® (XVIVO Perfusion) solution was gradually increased with a target of 40% of the estimated donor cardiac output. Functional assessment (PaO_2/FiO_2 in the pulmonary artery and vein, lung dynamic compliance and peak airway pressures) was performed hourly after 15 min of FiO_2 100% and 5min of lung recruitment with PEEP 10 mmHg. The reconditioning is performed at least for 2 hours, and maximum up to 4 hours. The lungs are considered suitable if the left atrial PaO_2/FiO_2 is > 400 mmHg and the other functional parameters (lung weight, compliance…) are stable or better. If the criteria for acceptance were not reached, lungs are considered unsuitable for transplantation and sent to the pathology department for analysis.
In the case of acceptance, the lungs remained on the perfusion system until explantation of the first lung onto the recipient. Then, the lung block was cooled down in the circuit to 10ºc in a 10-min period. The first lung was immediately transplanted and the second was statically preserved at 4ºc until transplantation.

2. SURGERY

The surgical technique consists usually of a sequential double-lung transplantation through two anterolateral thoracotomies(4).
Usually, the first lung transplanted is the one with least perfusion demonstrated by ventilation perfusion scan.
Unless, dissection is hemorrhagic, after discussion between surgeon and anesthesiologist, all patient received 50 IU.kg^{-1} of heparin at first pulmonary artery clamping or at ECMO implantation if the ECMO was implanted before the first pulmonary artery clamping. ECMO circuits are preheparizined, so clotting was not monitored, neither by ACT.

3. PLASMAPHERESIS

The decision to accept a graft is made according to the use of virtual cross-match (VCXM), performed according to preformed donor-specific antibodies (pf-DSA) detected on historical serum sampled at listing. Our policy is to allow allocation of a proposed graft to an immunized candidates in case of corresponding pf-DSA with mean fluorescence intensity (MFI) are between 500 and 5 000, whereas all pf-DSA > 5 000 MFI are considered as not permitted. For all these immunized lung transplant recipients with historical pf-DSA with MFI > 500 and < 5 000, one preoperative plasmapheresis session is performed just before surgery. The indication of desensitization treatment in these immunized lung transplant recipients is then readjusted at day-1 post-transplantation, according to the MFI results of pf-DSA detected on day-0 serum, sampled at the time of the transplantation. In case of detection of at least one immune-dominant DSA (iDSA) which remained >1 000 of MFI on day-0 serum, all patients undergo a desensitization protocol which included:

- perioperative plasmapheresis sessions (one performed immediately before transplantation, then 5 sessions over 5-10 following days; 2/3 fresh frozen plasma fibrinogen substitution if serum fibrinogen < 2 g.L-1) associated with
- rituximab (375 mg.m-2) at day-1 post-PE and;
- IVIg infusion (2 g-kg-1) at day-3 post-PE
- mycophenolate mofetil (3g per day.

For all patients with pf-DSA with MFI > 500 and < 5 000 on historical serum but with a immune-dominant DSA (iDSA) which remained < 1 000 of MFI at day-0, the desentization protocol is stopped at day-1, while they have already received 1 pre-transplantation plasmapheresis session.

When the plasmapheresis is indicated preoperatively, the anesthesiologist organizes it before patient's arrival to the post-operative care unit (PACU), in order to minimize the risk of delay of entrance in the operating room.
An 11F dialysis catheter is inserted under ultrasound in the left femoral vein.
A hemostatic assessment is then performed to control the absence of factor deficit.
The circuit is anticoagulated by citrate, and calcium is administrated at 1 mg.h-1 during the 2 hours duration of the plasmapheresis.
If the transplant is cancelled after performing the plasmapheresis, it is not necessary to repeat it during the next 36 hours.

1.1.1. Anesthetic management

Perioperative anesthetic management is fully standardized at our center. Our protocol was recently published(5).

1.4. Preoperative assessment

1.1.2. Preoperative anesthesia consultation

All patients included in the Foch Lung Transplant Program undergo on a preoperative anesthesia consultation for standard risk assessment and to inform the patient on the global risks and possible strategies to avoid them(6).
This consultation makes the synthesis of cardiovascular exams (transthoracic echocardiography, vascular ultrasonography of the supra-aortic trunks, right heart catheterization), lung function testing, screening of hemorrhagic and thrombotic disorders, nutrition status, anxiety and depression status.
If patient agrees, he could be part of a preoperative autohypnosis program in order to reduce postoperative anxiety and postoperative chronic pain(7).
These elements are then discussed in the final staff in order to determine the peri-operative final strategy.

1.1.3. Assessment the day of the surgery

The patient is welcomed in the post-anesthesia care unit (PACU).
The preoperative assessment combines:
- biological exams: serum electrolytes, blood count, hemostasis test (PT, APTT ratio, fibrinogen, thrombo-elastography), search for irregular agglutinins,
- transthoracic echocardiography (to search for a preoperative hypovolemia, a myocardial dysfunction, or a worsening in right heart function)
- chest X-ray

One respiratory physiotherapy session is performed when available for suppurative disease (cystic fibrosis, dilation of the bronchi).
Immunosuppression and antibiotic prophylaxis are defined preoperatively.
One hour before entry into the OR, patient receives Paracetamol 1g, Cimetidine 200mg and immunosuppressors. Per os Bromazepam 25 mg for anxiolysis is optional.

The nurse anesthetist team prepares all anesthetics drugs at confirmation of the transplantation prior patient entering the OR. The blood bank is contacted to ensure that blood products are available.

1.5. Intraoperative management

A senior anesthesiologist having a thorough knowledge of intraoperative management of lung transplantations, an anesthesiologist in training, a resident in anesthesia, and a nurse anesthetist are totally dedicated to the intraoperative care and are replaced by a new team at the end of their shift. In this way, not everyone involved in the transplantation activity is polluted by other operating activities, including emergencies.

1.1.4. Preemptive analgesia

A thoracic epidural catheter is inserted before induction of general anesthesia (T4-T6) in absence of contra-indication and perfused with a mixture of local anesthetic and opioid during surgery (levobupivacaine 1.25 mg mL-1 and sufentanil 0.25 µg.mL-1). The mixture is infused during surgery using a patient control epidural analgesia (Sapphire Epidural Infusion Pump, Hospira Infusion Systems), set as followed: background infusion 5ml.h-1, bolus of 3ml, lockout interval of 20min. If patient requires, a lite sedation by remifentanil (cerebral target infusion at 1 to 2 ng.mL-1) can be added. If the epidural catheter is contra-indicated, a multimodal analgesia is proposed by lidocain (1.5 mg.kg-1 bolus + 2 mg.kg-1.h-1 continuously) till the maximal recommended posology + ketamine (0.3 mg.kg-1 bolus + 0.2mg.kg-1.h-1 continuously). If a patient is successfully extubated at the end of surgery, a bilateral serratus anterior plane block catheter is inserted after chest closure(8). A high-frequency linear probe (L4-12t, 4,2-12 MHz, Vivid 7, GE Healthcare, Fairfield, Connecticut, USA) is immunosuppressive protocol and as methylprednisolone is administrated at high dose; dexamethasone is not added to prolonged the efficiency of the bloc. A background infusion of 7 mL.h-1 of levobupivacaine 1.25 mg.mL-1 is administrated to each side through the catheters (maximal cumulative doses of 2mg.kg-1.h-1).placed transversally and laterally to the incision. First, the 18-Gauge 80 mm Tuhoy needle (Portex, Smith Medical) is progressed in an anterior to posterior direction, in an in-plane position, until the superficial plane of the serratus muscle at the fifth rib middle axillary line. A single injection of 30 mL of levobupivacaine 2.5 mg.mL^{-1} is injected bilaterally to reach the maximal allowed doses of 2.5mg.kg^{-1}.

Secondly, an epidural catheter (Closed end Multiport, Portex, Smith Medical) threaded 3 cm is inserted through the Tuhoy needle. The same procedure is performed on the contralateral side with the same dose of local anesthetic. Due to the

1.1.5. Induction

The induction of anesthesia is a critical step in lung transplantation management. These patients have a poor pulmonary reserve associated to a little cardiac ability to adapt to relative hypovolemia (preoperative volemia status, vasoplegia, and reduced sytemic venous return due to anesthetic drugs vasodilation), to the increase of right heart afterload (mechanical ventilation, hypercabia), or to an insufficient myocardial contractility (anesthetic drugs, hypoxaemia in fragil right coronary artery). A special attention should be payed to the last chest CT scan in order to take in consideration the risk of pneumothorax (if giant bulla) o dynamic pulmonary hyperinflation (especially in obstructive disease).

Preoxygenation is delivered with facemask (FiO_2 = 100%) or with a humidified high flow nasal cannula (Optiflow™, Fisher & Paykel, New Zealand). Anesthetic induction consists on a rapid sequence induction with succinylcholine or rocuronium and total intra-venous anesthesia with propofol and remifentanil titration to maintain a bispectral index value (BIS Brain Monitoring, Covidien-Medtronic, Minneapolis, MN, USA) between 40 and 60. Myorelaxation maintainance is performed by atracurium. For suppurative disease, a single-lumen endotracheal tube is firstly inserted in order to perform therapeutic bronchoscopy for suctioning both native lungs, and secondly exchanged for a double-lumen endotracheal tube, using a tube exchanger (Cook® Airway Exchange Catheter – Extra-Firm with Soft Tip, Cook Medical Incorporated, Bloomington, IN, USA). Systematic control of double-lumen tube placement by a fiberoptic exam is performed.

1.1.6. Hemodynamic

Norepinephrine is systematically administered to counteract the vasodilation due to general anesthesia and epidural infusion. The initial dose is 0.03 $\mu g.kg^{-1}.min^{-1}$ and continuous infusion rate is adjusted to maintain a mean arterial pressure of 65 mmHg.
Intraoperative hemodynamic monitoring includes:
- a right radial arterial catheter (if impossible, insertion under ultrasound a brachial arterial catheter)(9),
- pulmonary artery catheterization (Edwards Lifesciences Corp., Irvine, CA, USA),
- and transesophageal echocardiography (TEE) (Vivid 7 and a multiplane probe 6.2 / 5.0 MHz, GE Healthcare, Fairfield, CT, USA)(10).

An initial TEE report is fulfill at the beginning of the surgery to precise:
- segmental and global kinetic disorders,
- evaluation of cardiac output (aortic or pulmonary VTI)
- evaluate right and left ventricular functions.
- look for valvular heart disease and intracavitary thrombus
- look for a patent foramen ovale by the color doppler then in case of obvious absence by a bubble test (sensitized by the release maneuver of PEEP).

Then the TEE is performed during maintenance of anesthesia to assess:
- volemia (and fluid responsiveness)
- right ventricule failure contemporary to the first and second pulmonary artery clamping test,
- arterial and venous pulmonary anastomosis when possible (11),
- and air embolism at graft pulmonary artery declamping

1.1.7. Bleeding and transfusion

Bleeding is prevented using an antifibrinolytic agent (tranexamic acid with a bolus dose of 30 $mg.kg^{-1}$ followed by a continuous infusion of 5 $mg.kg^{-1}.h^{-1}$). Cell salvage is used except in patients with cystic fibrosis(12).

The red blood cell transfusion is target to 10 $g.dL^{-1}$ of hemoglobin. Usually, fresh frozen plasma is transfused with a 1:1 ratio to red blood cell. Platelets are transfused when < 50 $G.L^{-1}$.

1.1.8. Ventilation settings

For restrictive syndrom, expiratory duration is reduced in order to adapt to the decrease compliance, I/E ratio is set at 1:1.5.
For obstructive syndrom, expiratory duration is prolonged in order to reduce trapping and risk of gas tamponade I/E ratio is set at 1:3. In case of unexplain hemodynamic failure, the ventilation circuit is disconnected.
For suppurative syndrom, ventilation may be extremely difficult despite an aggressive bronchial toilet. However, ventilation does not need to be protective as lungs are explanted rapidly.
Protective ventilation strategy(13) is used after first graft implantation including:
- low tidal volume based on ideal body weight (two-lung ventilation 6 $ml.kg^{-1}$, one-lung ventilation 4 $ml.kg^{-1}$) to reach a maximum plateau pressure of 30 cmH_2O;
- respiratory rate adapted with the objective of normocabnia or minimal respiratory acidosis (pH > 7.25);
- positive end expiratory pressure between 5 and 10 cm H_2O;
- Intermittent recruitment maneuvers are performed regularly to reduce atelectasis, in order to facilitate ventilation and to increasing oxygenation.

Inhaled nitric oxyde (iNO) was systematically administered during the procedure(14). It is started systematically just after control of positionning of the double-lumen tube at an initial concentration of 10 ppm, possibly modified in particular in case of impaired right ventricular function (maximal dose of 40 ppm). iNO is never stopped before the end of the procedure. iNO is delivered using OptiKINOX™, which is integrated into a mobile, ready-to-use treatment station with two tanks containing a gas mixture at a concentration of 450 ppm of NO (Air Liquide, 75321 Paris, France). OptiKINOX™ allows for a sequential administration of iNO during inspiration on the inspiratory limb of the ventilator and a targeted dose of FiO_2.

1.1.9. Graft implantation and pulmonary artery declamping

Pulmonary artery clamping is the second critical step because of the major increase in pulmonary vascular resistance. At this point a clamping trial is realized for 5 to 10 minutes before continuing the dissection. In case of hemodynamic failure a veno-arterial ECMO will be required:
- mean pulmonary artery increase associated with
- cardiac output decrease (right ventricle dilation, VTI decrease, or SvO2 decrease).

During lung implantation, volemia should be optimizing to limit hemodynamic repercussion of mediastinal manipulation by the surgeon, especially during the venous anastomosis.

The third critical step is the pulmonary artery declamping. Before each declamping:
- patient is placed in Trendelenburg position to prevent cerebral air embolism;
- systemic arterial pressure is optimized;
- endobronchial secretion are suctioned;
- reventilation at FiO2 = 100% (to minimize an eventual air embolism) during the first 10 minutes, followed by a rapid decreased to acheived a minimal SpO_2 > 92%;
- Vascular purge is performed anterogradely, declamping the pulmonary artery

At the recirculation, TEE is placed in the mid esophageal aortic valve long axis view (120º), ST segment is monitored in all derivations and ratio suppression of the BIS is observed. In case of a myocardial air embolism, blood pressure is elevated via norepinephrine and fluid support.
Secondly, a careful assessment of the venous anastomosis is performed with the TEE looking for venous diameters and velocities (< 1m.s-1). If the upper and lower donor pulmonary veins are not visualized, the surgeon can complete the assessment by a direct evaluation of the anastomosis, placing the high-resolution transducer 7 MHz (GE i13L probe; GE Healthcare) on the suture lines(11).

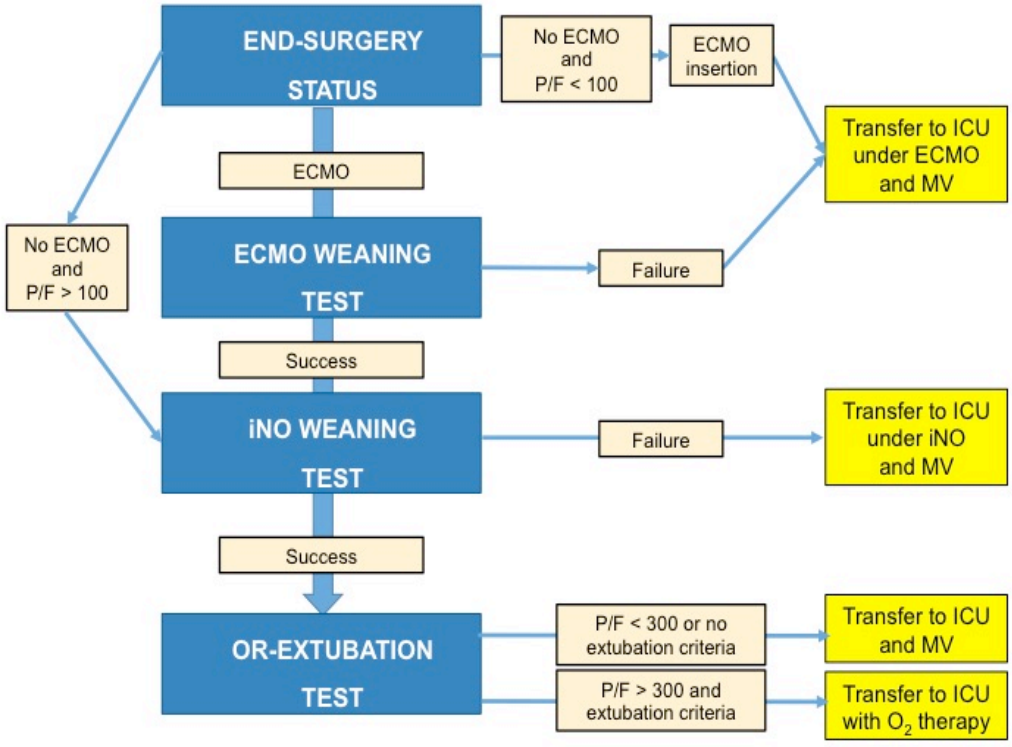
In case of a doubt on the arterial anastomosis, directly measuring pressures gradients are directly measured before and after the pulmonary artery anastomosis by needle puncture.
A special attention should be taken to avoid a supranormal cardiac output with high pulmonary blood flow and microvascular sheer forces. In some situations, a VA ECMO should be discussed.

1.1.10. ECMO management

Extracorporeal membrane oxygenation may be required before transplantation in cases of severe respiratory failure in patients on the waiting list or during surgery either caused by hemodynamic failure (e.g., right ventricular dysfunction, cardiac failure) or respiratory failure (e.g., severe hypercarbia or hypoxemia) refractory to standard medical treatment(15).
A 21-29F venous cannula and a 13-19F arterial cannula (HLS, Maquet Cadiopulmonary GmbH, Rastatt, Germany) are inserted at the surgeon's discretion peripherally rather than centrally under TEE control after a single bolus of 50 $IU.kg^{-1}$ heparin. In the case of peripheral femoro-femoral cannulation, an additional 7F cannula (CruraSave® Femoral-Perfusion Set, Freelife medical GmbH, Aachen, Germany) is systematically inserted into the superficial femoral artery and connected to the arterial branch of the ECMO circuit to ensure anterograde leg reperfusion and to prevent limb ischemia. ECMO was provided by the Permanent Life Support which consists in particular of a Rotaflow centrifugal pump and a PLS-i Oxygenator, Maquet Cardiopulmonary GmbH, Germany). The priming volume is saline 600 ml + unfractionated heparin 1 $IU.kg^{-1}$.
Before first graft implantation, ECMO is set at the maximum flow to decrease right heart load and ensure the maximal oxygenation, in order to avoid myocardial hypoxia.
After first graft implantation, ECMO is adjusted to the real cardiac outflow measured via TEE and Swan Ganz catheter. Pulmonary artery curve is maintained pulsatile and EtCO2 > 15 mmHg to limit warm ischemia.

1.6. End of the procedure

At the end of transplantation, hemodynamic and respiratory support is deescalated as feasibly as possible via a three-step weaning trial.



Three-step weaning trial

In patients needing an intraoperative ECMO, a 10 minutes weaning trial is performed by reducing the ECMO blood flow progressively to 1 - 1.5 $L.min^{-1}$ under clinical and echocardiography monitoring ("ECMO weaning test"). A positive test is defined as:

- a stable left ventricular outflow tract velocity time integral (LVOT VTI), and a mean arterial pressure above 60 mmHg with minimal dose of vasopressors and presence of a pulsatile arterial waveform after ECMO blood flow reduction,
- and a PaO_2/FiO_2 ratio > 200 with FiO_2 = 40 % on the ECMO and FiO_2 < 50% on the ventilator. In case of a positive weaning test, ECMO cannulas are removed by the surgeons before ICU transfer. When the surgical procedure is performed without ECMO, the PaO_2/FiO_2 ratio is calculated at the end of surgery and the following steps are undertaken:
- if the PaO_2/FiO_2 ratio is lower than 100 at the end of the procedure, ECMO is instituted before transferring the patient to the ICU;
- if the PaO_2/FiO_2 ratio is greater than 100, a "iNO weaning test" is performed. iNO is reintroduced in case of substantial decrease in PaO_2, or worsening of the right ventricular function as evaluated on TEE and patients are transferred to the ICU under mechanical ventilation and iNO. For patients whose weaning test of inhaled nitric oxide is a success, a new PaO_2/ FiO_2 ratio is calculated after stopping iNO therapy. OR-extubation and a "non-invasive attempt" are performed if:

- PaO_2/FiO_2 ratio is greater than 300 and,
- $PaCO_2$ is below 50 mmHg,
- temperature is above 36ºc,
- there is no hemodynamic failure,
- lactate level is below 3 $mmol.L^{-1}$,
- mixed SvO_2 is greater than 65%,
- there is an absence of active bleeding through drains,
- there is an absence of bleeding from bronchial aspirations,
- there is an absence of coagulation disorders,
- and hemoglobin blood level is greater than 10 $g.dL^{-1}$.

Weaning trial was performed via a double lumen tube like an elective thoracic surgery, after interruption of iv anesthetic agents. The "non-invasive ventilation attempt" consisted on a 20 minutes, period of non-invasive ventilation in an awake and calm patient, using face-mask and a specific ventilator with inspiratory and expiratory airway pressures are 8 and 4 cmH_2O, with a FiO_2 = 100%, and adapted to patient, comfort. If the attempt is successful, patients is then transferred to the ICU with a high concentration oxygen facemask to the ICU. Otherwise, the patients is anesthetized and re-intubated with a single-lumen tube, using a tube exchanger (Cook® Airway Exchange Catheter – Extra-Firm with Soft Tip, Cook Medical Incorporated, Bloomington, IN, USA) before transfer to the ICU under mechanical ventilation.

4. ICU MANAGEMENT

All extubated patients are placed on non-invasive ventilation for at least six hours following ICU admission. The initial settings for inspiratory and expiratory airway pressures are 8 and 4 cmH_2O, respectively, with a FiO2 = 100%. The settings are then adjusted according to clinical judgment and arterial blood gas. During the following 24 hours, non-invasive ventilation is continued for at least one hour every four hours and later adjusted to patients respiratory status. Extubation in the ICU is decided by the attending intensive care physician. Grade 3 primary graft dysfunction is defined as a PaO_2/FiO_2 ratio < 200 at 72 hours after transplantation, without evidence of pulmonary infection or any other specific cause(16).

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