MedCrave
Step into the World of Research

Journal of Pediatrics & Neonatal Care

Research Article

Open Access

CrossMark

Inter hospital transfer of critically ill neonates-challenges faced

Abstract

This article focus to assist medical practitioners and hospitals develop and implement strategies and protocols for the safe transport of critically ill patients. The goal of this document is to minimise risks and maximise safety for patients during transport.

We searched the Cochrane library, MEDLINE and EMBASE databases, and references lists of identified studies.

A large number of inter hospital transfers already take place and the number is likely to increase. It is essential that a systematic approach is taken to the process of patient transfer; starting with the decision to transfer, through the pre-transfer stabilisation, and then the management of the transfer itself. The transport of critically ill patients carries inherent risks. These guidelines promote measures to ensure safe patient transport. Although inter hospital transport must comply with regulations, we believe that patient safety is enhanced during transport by establishing an organized, efficient process supported by appropriate equipment and personnel.

Keywords: inter-hospital transport, mode of transport, paediatric emergency, septic shock, critically ill patient transport, delay in transport

Volume 6 Issue 2 - 2017

Pradyumna Pan
Ashish Hospital and research Center, India

Correspondence: Pradyumna Pan, Ashish Hospital and research center, Home science college road, Napier Town, Jabalpur, India, Tel 9893322160, Email dr_pan@rediffmail.com

Received: July 01, 2016 | **Published:** January 24, 2017

Introduction

Treatment of the sick neonate in specialized neonatal intensive care units has been associated with decrease in mortality and morbidity. Organized emergency neonatal transport systems developed and became an important component in the regionalization of perinatal care.[1–4] In utero transfer is the safest transfer but unfortunately, preterm delivery, perinatal illness and congenital malformations cannot always be anticipated, resulting in a continued need for transfer of babies after delivery.[5] These babies are often critically ill, and the outcome is partly dependent on the effectiveness of the transport system.[6] Facilities for neonatal transport in India are dismal. Most neonates are transported without any pre-transport stabilization or care during transport. Any available vehicle is used which often takes long hours to reach.

With less experienced staff, the risk of adverse events on such transports can be greater than with well equipped and trained staff.[7–9] Many of the babies thus transported are cold, blue and hypoglycemic and 75% of the babies transferred this way have serious clinical implications.[10–12]

An attempt has been made to address the following questions regarding neonatal transport:

Why transport of sick neonates is necessary?

Transportation of the sick or preterm babies to a centre with expertise and facilities for the provision of multi-organ intensive care has been shown to improve outcomes.[13] Prematurity, asphyxia and sepsis are the most common cause of neonatal mortality.[14] Many of these are easy to correct and a significant decrease in neonatal mortality can occur if specialized care can be made available to these neonates. Patients may be transferred from the emergency department, critical care units, operating theatres, wards or other areas of the hospital. Transfers often occur outside of normal working hours and take place at short notice.[15]

What is the difference between self transport and organized transport?

Organized transport service provides almost the same level of monitoring and the quality of care during the transport that is available in the advanced care facility. Ideally it should have the ability to provide mechanical ventilation, multiple fluid infusion therapy and cardio-respiratory monitoring. In India, most sick neonates are transferred by their parents or paramedical personnel either in private vehicles or poorly equipped ambulance. There is currently no dedicated neonatal transport service provided by the states in India.

Evidence

There is enough data to suggest that the transport by a skilled organized team reduces neonatal mortality and morbidity.[16] Neonates transported by the hospital team had significantly higher survival as compared to those who came on their own.[17]

Principals of transport

Pre-transport stabilization and care during transport are the two pillars of care during transfer of critical ill patient.

Hypoglycaemia, hypothermia, poor perfusion and hypoxia have been shown to be associated with high mortality in transported neonates. TOPS (**T**emperature, **O**xygenation, **P**erfusion, **S**ugar) a simplified assessment of neonatal acute physiology gives a good prediction of mortality in these neonates. Prior stabilization and adequate care during transport results in decrease of hypoglycaemia, acidosis and mortality.

How should one communicate for neonatal transport?

When a child that requires transport is decided, the team for the sending centre contacts by phone the centre where the child will be

transported. The conversation will be held by the highest level persons from the two centres .The transferring hospital has the responsibility to equilibrate the child till the transfer team comes.

The transport documentation

The hospital from which the transfer is made has the obligation to provide the transport team the following medical documents:

The medical record of the patient in original .The transfer paper as detailed as possible, containing data about parents, maternal history, current pregnancy, birth process, the child status at birth, intensive care measures and all the investigations done. If the transport team requests, x-rays, ultrasounds and other investigations results should be released in original. If some laboratory test's results are not yet finished at the moment of transfer, the results will be send to the receiving hospital as soon as they became available.

The discussion with the family

Transport is permitted only with the family consent.[18–19] The family should be explained about the child status, the transport risk and benefits. The family has the right to refuse the transport.

Stabilisation before transfer

Although transfers are potentially associated with additional risk to patients, they can be safely accomplished even in extremely ill patients.[20] Generally, a transfer should not be undertaken until the patient has been resuscitated and stabilised.

There is a consensus that in order to have a good quality transport a good equilibration before transport is required.

The stabilization before the transport is done by the team of the hospital where the child was born, with the following objectives:

1. To assure and maintain the temperature.

It is accepted as normal newborn temperature a value of the central temperature (rectal or axillary) of 36.5-37.5 °C . This is the value of the temperature equilibrium for which the energy consumption needed for keeping it is minimum.[21–22]

2. To assure the respiratory equilibrium.

Most critically ill neonates who require transfer to a neonatal intensive care unit have existing different degree of hypoxia, respiratory distress or impending respiratory failure, either as a primary diagnosis or secondary to their primary disease process.

The patient is evaluated from the point of view of the respiratory distress.

The team should be capable of (a) Recognizing impending respiratory failure, (b) Performing effective bag-valve-mask ventilation, (c) Performing atraumatic intubation with appropriate endotracheal tubes, (d) Instillation of artificial surfactant, and (e) Management of ventilator settings. In case of respiratory distress oxygen under tent will be given to the neonates. In patients who require positive pressure ventilatory assistance, the first level of intervention is bag-valve-mask ventilation, although it is unacceptable for prolonged airway management during transport.

3. To assure the cardio-vascular equilibrium

The baby should have at least one vein punctured and a perfusion is installed. Assess perfusion for warm peripheries, capillary refill time of ≤3seconds, tone and activity, and blood pressure. Stabilize perfusion before moving the baby to the ambulance. Syringe pumps are required to use inotropes with accuracy. Continuous Pulse oximeter monitoring is preferable.

4. To assure the metabolic equilibrium and the glycemia.

The normal glucose in blood is 40mg/dl. The following categories of children present a risk of hypoglycemia: newborns from diabetic mothers big for their gestational age, newborn that are small for their gestational age small premature, sepsis or in shock newborns.

For all these newborns the glucose will be checked through rapid tests every 2hours. The glycemia is monitored continuously.[23,24]

Special considerations regarding pre-transport stabilization for some pathology

Abdominal wall defects (Omphalocele, Gastroschisis): An oro-gastric drainage should be installed. The abdominal defect to be covered with soft, sterile sheets. Optional, the sheets may be wet with warm physiologic saline. Also, a special plastic cover may limit the heat losses.

Defects of the neural tube (bifida spine): The defect to be covered with soft, sterile sheets. Optional, the sheets may be wet with warm physiologic solution. Also, a special plastic cover may limit the heat losses.

Diaphragmatic Hernia: it is compulsory to put the child on oro-tracheal intubation and naso gastric drainage.

Other malformations of the digestive tube: Nasogastric aspiration should be installed.

Esophageal Atresia/Tracheoesophageal fistula: aspiration should be started and maintained.[25,26]

Accompanying the patient

A critically ill patient should be accompanied by a minimum of two attendants. The precise requirement for accompanying personnel will depend upon the clinical circumstances in each case.

Levels of patients' critical care

The decision should be made by a senior doctor[26]

Level 0: Patients whose needs can be met through normal care should not usually need to be accompanied by a doctor, nurse or paramedic.

Level 1: At risk of their condition deteriorating, support from the critical care team will require a paramedic ambulance crew and may require a nurse, paramedic and/or medical escort.

Level 2: Requiring more detailed observation or intervention including support for a single failing organ system or post-operative care must be escorted by competent, trained and experienced personnel, usually a doctor and a nurse or paramedic.

Level 3: Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. These patients must be escorted by competent, trained and experienced personnel, usually a doctor and a nurse or paramedic.

All individuals involved in the transport of critically ill patients should be suitably competent, trained and experienced.

Monitoring, drugs and equipment

Patients with level 1, 2 or 3 critical care needs will require monitoring during the transfer. Monitoring needs to be established

and secure before the transfer is started. The personnel involved in the transfer should check that they have adequate supplies of the necessary drugs. These may include sedatives, analgesics, muscle relaxants, and inotropes. Many of these drugs are best prepared before hand in pre-filled syringes. All equipment should be robust, durable and lightweight. Electrical equipment must be designed to function on battery when not plugged into the mains. Additional batteries should be carried in case of power failure. Portable monitors should have a clear illuminated display Portable mechanical ventilators should have minimum connection, disconnection and high pressure alarms. It should be able to supply positive end expiratory pressure and variable inspired oxygen concentration, respiratory rate, inspiratory: expiratory ratio and tidal volume.

The ambulance

The European Committee for Standardisation has published specifications for ambulances. Private transport services may use Type C mobile ICU vehicles. These will have 240V AC power, a secure critical care trolley, a ventilator, monitors and syringe pumps. It is more usual to request an ambulance from the local ambulance service to perform the transfer. This is a likely to be a Type B or equivalent vehicle that has 12V electric sockets, oxygen supply and limited monitoring and other equipment. The oxygen supply and battery operated equipment must be more than sufficient for the anticipated duration of the transfer.

A major issue relating to safety during transport is the speed of travel. For the majority of cases high-speed travel is not necessary and the safety of all passengers and other road users is paramount, the goal is to facilitate a smooth and rapid transfer with the minimum acceleration and deceleration. While safety is of paramount importance during transfer, there is always a remote possibility of an ambulance being involved in an accident resulting in death or serious injury to staff.

What care should be given during transport?

Temperature maintenance: Use a transport incubator if available. Kangaroo mother care (KMC) by mother or attendant is a useful way to maintain temperature. Kangaroo mother care is a good method of temperature maintenance during transport especially in resource limited conditions when transport incubators are not available. Other methods like adequately covering the baby, and using improvised containers (Thermocol box, basket, polythene covering) may help in maintaining temperature.

Airway and breathing: Keep neck of the baby in slight extension position. If airway is unstable, it is better to intubate and transport, if intubation is not considered necessary /possible, short PPV or CPAP can be provided using a T-piece resuscitator.

Circulation: Assess perfusion for warm peripheries, capillary refill time of ≤3seconds, tone and activity, and blood pressure. Syringe pumps are required to use inotropes with accuracy. IV fluids should be continued, perfusion solution and volume should be according to the need of the baby. Continuous Pulse oximeter monitoring is preferable.

Communication: Inform SCNU / NICU to arrange and organize baby cot and keep the over head radiant warmer on.

Feeds: It is best not to attempt feed sick babies with abnormal sensorium or severe respiratory distress before or during transfer. A well baby at risk of hypoglycemia may be fed in addition to intra venous fluid. If baby can accept provide breast feeds, if not give expressed breast milk (EBM) with spoon. If EBM not available give any available milk. During feeding ambulance should be stopped.

What are the different modes of transport?

The choice of vehicle will depend upon clinical urgency, travelling distance, weather conditions and its availability.

Road Ambulance: Better suited for distance of 10- 200kms .It has advantages of relatively easily available, lower costs, least influenced by weather, more space and better patient access. Can be stopped or diverted to the nearest hospital if necessary for any emergency interventions. Disadvantages being transport time is influenced by speed limitations, traffic delays and road conditions.

Rotary Wing (helicopter): For distance from 50- 300kms .Advantages are speedy retrieval and better utilizations of medical staffs. Disadvantages are high costs, limited space, may be influenced by weather conditions, require a landing site close to the hospital, limited patients access, high noise and vibration levels.

Fixed Wing Aircraft: Being good for long distance retrievals, advantages being reasonable space and access to patient, family can travel with their baby. Disadvantages are require nearby airport, immigration clearance, longer retrieval time and assistance with road transport.

Air transport exposes patients and crew to particular risks including:

Reduced oxygen partial pressure, the need for pressurisation to sea level when clinically indicated, risk of rapid depressurisation ,expansion of air filled cavities both within the patient and the equipment, such as endotracheal tube cuff, middle ear, air-filled spaces under airtight dressings etc, limb swelling beneath plaster casts, worsening of air embolism or decompression sickness, limited space, lighting and facilities for interventions, noise, extremes of temperature, extremes of humidity, acceleration, deceleration and turbulence, vibration, electromagnetic interference between avionics and monitoring devices, danger from loose and mobile equipment.[27–29]

How should the family be supported during transport process?

Families of the sick newborn are under considerable stress, and the transport team can provide sensitive support. Parents need accurate information about the neonatal clinical condition and prognosis, and an opportunity to ask and have questions answered by the team.

Documentation and handover

Clear records should be maintained at all stages. This is a legal requirement and should include details of the patient's condition, reason for transfer, names of referring and accepting consultants, clinical status prior to transfer and details of vital signs, clinical events and therapy given during transport.

On arrival at the receiving hospital, there should be a formal handover between the transport team and the receiving medical and nursing staff who will assume responsibility for the patient's care. Handover should include a verbal and written account of the patient's history, vital signs, therapy and significant clinical events during transport. X-rays, scans and other.

What should be done in case the neonate deteriorates during transport?

The most appropriate action depends on the level of skills of transport team in resuscitation, space and equipments available in the ambulance, and the distance from the receiving hospital.

The two major strategies can be used in case of acute deterioration are:

- Stop the vehicle and resuscitate if skills and space is available.
- Don't perform any procedure in a moving vehicle; get to the nearest hospital, stabilize, before proceeding further.

What are the medico-legal issues associated with transport?

Most medico-legal problems are a result of poor communication and provision of inadequate information. The condition of baby, risks involved during transport, financial implications of transport and treatment at the referral centre should be discussed with family and documented and recorded.

If baby dies during transport: The ambulance should be stopped and CPR should be performed as per NRP guideline, then should be first taken to the higher health facility and casualty admission should be done. Parents should b explained and death certificate to be issued by the medical personnel of higher health centre .It is the responsibility of transporting team to make death certificate of baby.

Checklist

Do attendants have adequate competencies, experience, knowledge of case, clothing, insurance, appropriate equipment and drugs. Batteries checked, sufficient oxygen, trolley available, ambulance service aware or ready, bed confirmed. Case notes, X ray films, results and transfer chart prepared. Portable phone charged, contact numbers known, estimated time of arrival notified, return arrangements checked. Relatives informed, patient stable, fully investigated, monitoring attached and working. Drugs, pumps, lines rationalised and secured, adequate sedation, still stable after transfer to mobile equipment.

Summary of recommendations

I. The development of efficient transport systems is crucial to the implementation of regionalization of perinatal care.

II. Transportation of the sick or preterm babies to a centre with expertise and facilities for the provision of multi-organ intensive care improve outcomes.

III. Neonates needing special or intensive care should preferably be transported by a skilled transport team through an organized teamwork.

IV. Appropriate equipments and vehicle customized for neonates should be available for safe transport.

V. Pre-transport stabilization is the most vital step in the whole process of transport.

VI. Adequate and timely communication with the family, referring hospital and the support group is essential.[30–56]

Acknowledgments

None.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

References

1. Segal S. Transfer of a premature or other high-risk newborn infant to a referral hospital. *Pediatr Clin North Am*. 1996;13(4):1195−1205.
2. Segal S (Ed). Manual for the transport of high risk newborn infants. Canadian Pediatric Society . 1972. p.167−174.
3. Recommended standards for maternity and newborn care. Health and Welfare Canada.
4. Family centred maternity and newborn care. National Guidelines. *Health and Welfare Canada.* 1988.
5. Guidelines for perinatal care. (5th edn), American Academy of Pediatrics/American College of Obstetricians and Gynecologists. 2002.
6. Kempley ST, Sinha AK. Census of neonatal transfers in London and the South East of England. *Arch Dis Child Fetal Neonatal Ed* . 2004;89(6):F521−F526.
7. Rashid A, Bhuta T, Berry A. A regionalized transport service, the way ahead? *Arch Dis Child.* 1999; 80(5): 488- 492.
8. Cornette L. Contemporary neonatal transport: problems and solutions Arch Dis Child Fetal Neonatal Ed. 2004; 89(3):F212−F214.
9. Cornette L. Transporting the sick neonate. *Current Pediatr* . 2004;14:20−25.
10. Parmanum J, Field D, Rennie J, et al. National census of availability of neonatal intensive care. *BMJ*. 2000;321:727−729.
11. Britto J, Nadel S, Maconochie I, et al. Morbidity and severity of illness during interhospital transfer: impact of a specialized pediatric retrieval team. *BMJ* . 1995;311(7009):836−839.
12. Agostino R, Fenton AC, Kollée LAA. Organization of neonatal transport in Europe. *Prenat Neonatal Med*. 1999;4:20−34.
13. Leslie AJ, Stephenson TJ. Audit of neonatal intensive care transport: closing the loop. *Acta Pediatr*. 1997;86(11):1253−1256.
14. Orr RA, Felmet KA, Han Y, et al. Pediatric specialized transport teams are associated with improved outcomes. *Pediatrics*. 2009;124(1):381−383.
15. Bang AT, Bang RA, Baitule SB, et al. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet.* 1999;1354:1955−1961.
16. GrayA, Gill S, Airey M, et al. Descriptive epidemiology of adult critical care transfers from the emergency department. *Emerg Med J* . 2003;20(3)**:**242−246.
17. Chance G, Matthew J, Gash J, et al. Neonatal transport: a controlled study of skilled assistance. Mortality and morbidity of neonates less than 1.5 kg birth weight. *J Pediatr*. 1978;93(4):662−66
18. Temperature regulation. In: Gamella TL (Ed), Neonatology. *Appleton & Lange*, Norwalk, USA. 1999.
19. American Academy of Pediatrics, The American College of Obstetricians and Gynecologists Guidelines for Perinatal Care, (4th edn), Lybrary of Congress, USA. 1992.
20. Bose KL. Neonatal transport. In: Avery GB, et al. (Ed), Neonatology; Pathophysiology and Management of the Newborn, Fifth Edition, Lippincott Williams & Wilkins, Philadelphia. 1999; 35−48.
21. Baumgart S, Harrsch SC, Touch SM. Thermal Regulation. In: Avery GB, et al. (Eds), Neonatology; Patophysiology and Management of the Newborn, (5th edn), *Lippincott & Williams* Philadelphia. 1999;395−408.
22. Karlsen KA (Ed). Transporting newborns in the STABLE way. A manual for community hospital caregivers: pre-transport stabilization of the sick newborns, STABLE Program, Park City Utah, USA. 2001.
23. Jameson PP, Lawler PG. Transfer of critically ill patients in the Northern region. *Anaesthesi*a. 2000;55(5)**:** 489.

24. Mackenzie PA, Smith EA, Wallace PG. Transfer of adults between intensive care units in the United Kingdom: postal survey. *British Medical Journal.* 1997;314(7092)**:**1455−1456.

25. Spencer C, Watkinson P, McCluskey A. Training and assessment of competency of trainees in the transfer of critically ill patients. *Anaesthesia*. 2004;59(1):1248−1249.

26. NETS WA Manual Newborn Services Clinical Guideline.

27. The Intensive Care Society. Levels of critical care for adult patients. London, *The Intensive Care Society*. 2002.

28. Diaz MA, Hendey GW, Bivins HG. When is the helicopter faster? A comparison of helicopter and ground ambulance transport times. *The Journal of Trauma.* 2005;58(1)**:**148−153.

29. Dewhurst AT, Farrar D, Walker C, et al. Medical repatriation via fixed-wing air ambulance: a review of patient characteristics and adverse events. *Anaesthesia*. 2001;56(9)**:**882−887.

30. Day S, McCloskey K, Orr R, et al. Pediatric interhospital critical care transport: consensus of a national leadership conference. *Pediatrics*. 1991;4: 696−704.

31. Lee SK, Zupancic JAF, Sale J, et al. Cost-effectiveness and choice of infant transport systems. *Med Care.* 2002;40(8):705−716.

32. Lee SK, Zupancic JAF, Pendray MR, et al. Transport risk index of physiologic stability: a practical system for assessing infant transport care. *J Pediatr.* 2001;139(2):220−226.

33. King BR, King TM, Foster RL, et al. Pediatric and neonatal transport teams with and without a physician: a comparison of outcomes and interventions. *Pediatr Emerg Care*. 2007;23(2):77−82.

34. Shenai JP, Johnson GE, Varney RV. Mechanical vibration in neonatal transport. *Pediatrics*. 1981;68(1):55.

35. BS EN 1789. Medical vehicles and their equipment. Road ambulances. *British Standards Institute, London*. 2007.

36. BS EN 13976-1. Rescue systems. Transportation of incubators. Interface conditions. *British Standards Institute London*. 2004. 2003.

37. Carmichael A, McCullough S, Kempley ST. Critical dependence of acetate thermal mattress on gel activation temperature. *Arch Dis Child*. 2007;92(1): F44−F55.

38. Karlsen K. The STABLE Program. Utah, USA. 2001.

39. Transporting newborns the SAFER way. National Neonatology Forum of India, PENN India Health Group, University of Pennsylvania, WHO Perinatal Collaborating Center, Illinois. 1999.

40. Mathur NB, Arora D. Role of TOPS (a simplified assessment of neonatal acute physiology) in predicting mortality in transported neonates. *Acta Pædiatr.* 2007;96(2):172−175.

41. Sehgal A, Roy MS, Dubey NK, et al. Factors contributing to outcome in newborn delivered out of hospital and referred to a teaching institution. *Indian Pediatr.* 2001;38(11):1289−1294.

42. Daga SR, Daga AS, Dighole RV, et al. Rural neonatal care: Dahanu experience. *Indian Pediatr* . 1992;29(2):189−194.

43. McCall EM, Alderdice F, Halliday HL,et al. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. *Cochrane Database of Syst Rev*. 2008; (1):CD004210.

44. Neonatal transferal and transportation: NNF Training module. (Eds), Saluja S, et al. *National Neonatology Forum*, New Delhi. 2005.

45. Conde-Agudelo A, Diaz Rossello JL, Belizan JM. Kangaroo mother care to reduce morbidity and mortality in low birth weight infants. *Cochrane Database Syst Rev*. 2003;(4):CD002771.

46. Teitel D, Rudolph AM. Perinatal oxygen delivery and cardiac function. *Adv Pediatr*. 1985;32:321−347.

47. Fenton AC, Leslie A, Skeoch CH. Optimising neonatal transfer. *Arch Dis Child Fetal Neonatal Ed* . 2004;89:F215−F219.

48. Bowman E, Doyle LW, Murton LJ, et al. Increased mortality of preterm infants transferred between tertiary perinatal centres. *BMJ*. 1988;297(6656):1098−1100.

49. Gajendragadkar G, Boyd JA, Potter DW, et al. Mechanical vibration in neonatal transport: a randomized study of different mattresses. *J Perinatol.* 2000;20(5):307−310.

50. Buckland L, Austin N, Jackson A, et al. Excessive exposure of sick neonates to sound during transport. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88: F513-F516.

51. Campbell AN, Lightstone AD, Smith JM, et al. Mechanical vibration and sound levels experienced in neonatal transport. *Am J Dis Child.* 1994;138(10):967−970.

52. Bomont RK, Cheema IU. Use of nasal continuous positive airway pressure during neonatal transfers. *Arch Dis Child Fetal Neonatal Ed* . 2006;91(2): F85–F89.

53. Johannigman JA, Branson RD, Johnson DJ, et al. Out-of-hospital Ventilation: Bag-Valve Device vs Transport Ventilator. *Acad Emerg Med*. 1995;2(8):719−724.

54. Costakos D, Allen D, Krauss A, et al. Surfactant therapy prior to interhospital transport of preterm infants. *Am J Perinatol* . 1996;13:309−316.

55. Mildenhall LF, Pavuluri NN, Bowman ED. Safety of synthetic surfactant use before preterm newborn transport. *J Paediatr Child Health*. 1999;35(6):530−535.

56. The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant-the judgment of OSIRIS. *Lancet.* 1992;340(8832):1363−1369.