Intracardiac air — the 'hospital killer' identified?

Case reports and review of the literature

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Venous access is an essential part of caring for the sick neonate. The primary problem with catheters, whether peripherally or centrally placed, is the difficulty in maintaining them, the development of phlebitis and systemic infection, and fluid extravasation. A lesser known complication is the development of venous air embolism (VAE), as described in the 4 cases presented. We agree with others that VAE in newborn infants may occur more frequently than expected and emphasise the fact that it is preventable and that careful attention must be given to the techniques of preparing venous infusions. As health professionals (medical and nursing) we should take a harder line and regard these events as medically negligent until proven otherwise. We should take full responsibility for equipment, the connections, the infusate and the monitoring thereof.

Unfortunately, the prognosis for this condition remains poor and it is unclear whether an increased awareness of this condition would influence outcome. Manufacturers of intravenous fluids should produce products devoid of air in order to reduce the risk of venous air embolism.

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During 2000, a national newspaper reported on an unidentified 'hospital killer' stalking babies in some hospitals in South Africa.[1] According to the report, six infants had died since 1992 and two had recovered with brain damage following 'severe' reactions to drips.[1,2] Subsequently the Medicines Control Council appealed to doctors and hospitals to report similar cases.[2] Some pharmaceutical companies withdrew their infusion sets and solutions, and scrutinised and tested their products for compliance with safety standards, sterility and pyrogenicity, yet no aetiology was identified. An Intravenous Fluid Investigative Task Team was appointed by the Minister of Health and the team proposed a case definition for reporting these events: 'An untoward and unexpected reaction in a neonate which occurred soon after commencement of an intravenous (IV) infusion of standard neonatal maintenance solutions without any additives having been administered at the same time'.[2] The Task Force did consider air embolism as a distinctly possible cause, but could provide no evidence to substantiate the contention.

In the following narrative the authors present four cases in which causality is demonstrated between the patients' sudden clinical deterioration and subsequent death, intracardiac air and the citing of a peripheral venous line or an infusion pump that alarmed. We speculate that the accidental infusion of air from infusion sets may be at the root of the so far inexplicable acute clinical deterioration that some infants experience after a drip has been inserted.

Case reports

Case 1

A male infant with a birth weight of 1 770 g was born by normal vaginal delivery at 31 weeks' gestation. The infant manifested significant respiratory distress from birth. Initial chest radiograph confirmed severe respiratory distress syndrome (RDS). A peripheral intravenous infusion was inserted and infusion of Neolyte (Intramed, South Africa) was initiated. The infant was intubated and transported to the neonatal intensive care unit for mechanical ventilation. *En route*, the infant's skin turned blue-black with blotchy redness. The feet were extremely pale. The attending physician thought that this was a 'reaction' to the intravenous fluid and replaced it with 0.2% saline and glucose 5%. Over the next 10 minutes central perfusion returned to normal, but the hands and feet remained bluish. At this time an umbilical venous line was inserted. No air could be withdrawn. The infant's condition stabilised. Over the next 4 hours his mean blood pressure varied between 30 and 48 mmHg and his pulse rate between 150 and 165/min. He received surfactant treatment and routine intravenous penicillin. An anteroposterior chest radiograph did not reveal the classic picture of a pneumothorax or pneumopericardium. However, an area of hyperlucency was noted behind/within the left cardiac border (Fig.1). An anterolateral chest radiograph revealed the presence of air in the retrosternal area, anterior to the heart, as well as a hyperlucent area within the heart border. In the retrocardiac

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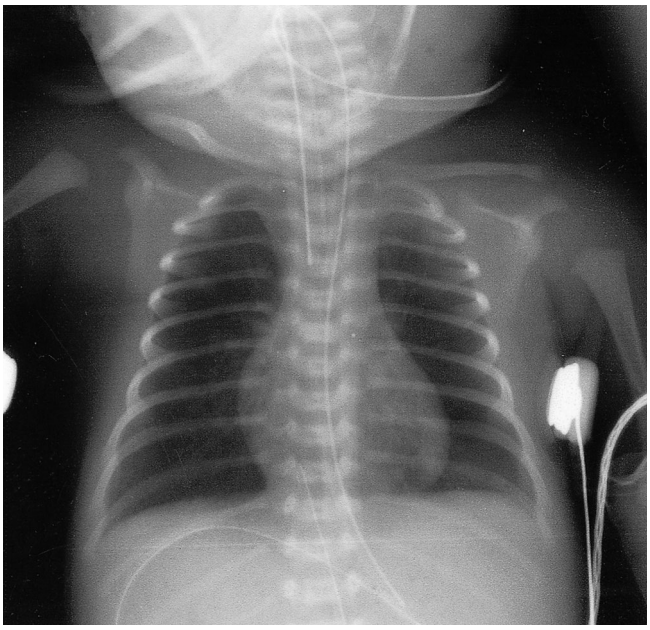

Fig. 1. Anteroposterior chest radiograph: No evidence for pneumothorax or pneumopericardium. An area of hyperlucency is noted behind/within the left cardiac border.

area a triangular shadow, representing aerated lung or free air, was present. A diagnosis of a pneumomediastinum and intracardiac air was entertained. The infant's clinical condition stabilised, but within 24 hours of birth he developed generalised myoclonic convulsive movements of all four limbs and was treated with phenobarbitone. The cranial ultrasound scan showed striking evidence of cerebral air embolism (Fig. 2), as manifested by an echogenic density in the right lateral

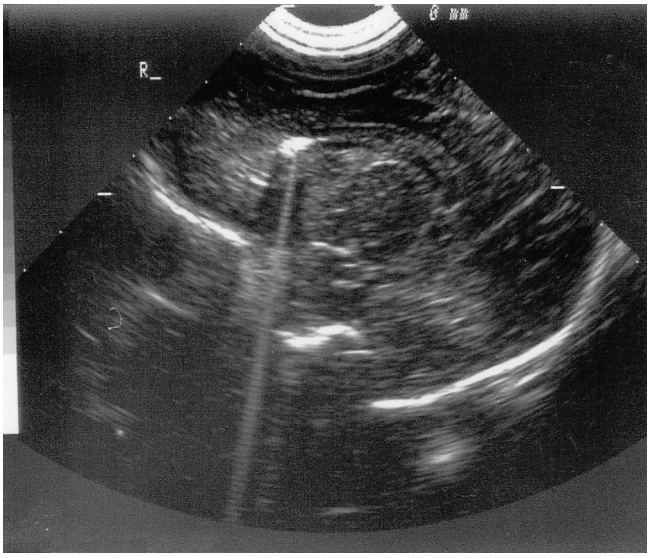

Fig. 2. Cranial ultrasonography evidence of cerebral air embolisation. An echogenic density in the right lateral ventricle created acoustic shadowing with no through transmission.

ventricle, which created an acoustic shadow with no through transmission.[3] A C-reactive protein and a blood culture were negative. On day 3 of life, the infant developed generalised oedema and a metabolic acidosis, followed by a severe acute pulmonary haemorrhage. Despite extensive resuscitation efforts the infant died. An autopsy was refused.

Case 2

A female infant was born by normal vaginal delivery at a gestational age of 34 weeks in a peripheral hospital. The infant was small for gestation, weighing 1 760 g. The mother tested positive for retrovirus and syphilis. Both she and the infant received treatment with nevirapine and penicillin. The infant developed respiratory distress, and nasal continuous positive airway pressure (nCPAP) was initiated. A chest radiograph supported the diagnosis of moderate RDS. Owing to respiratory deterioration, the infant was transferred to the tertiary hospital for mechanical ventilation. At the postnatal age of 5 hours the infant received exogenous surfactant. Within the next 4 days she was weaned to nCPAP. On day 6 of life the infant developed abdominal distension. The clinical picture was that of necrotising enterocolitis. The abdominal X-ray showed free peritoneal air. At laparotomy a bowel perforation at the terminal ileum was confirmed. The area was resected and a re-anastomosis was performed. Ten hours after the operation the infant 'collapsed'. Before this 'collapse', the attending nurse noted that one of the infusion pumps connected to a peripheral venous infusion line had alarmed. The infant appeared to be in shock. Her head was congested and cyanosed. Her torso was pale, more so on the right side than on the left. Owing to a decrease in breath sounds a diagnosis of a right-sided pneumothorax was entertained. An underwater drain was inserted before a chest X-ray was obtained. The shock-like appearance was not relieved. Another drain was inserted in the left pleural space, again without clinical improvement. The infant developed a bradycardia and blood gas drawn from the left tibialis posterior artery revealed frothy/foamy blood. A chest X-ray showed possible air within the pericardium on the right side of the heart as well as a hyperlucent area within the left cardiac border. Both lung fields were opacified and there was no evidence of pneumothorax. Despite resuscitation the infant died. A forensic pathological examination was performed which confirmed the presence of air in the right ventricle.

Case 3

A male infant was born via a caesarean section because of fetal distress at 27 weeks' gestation. He weighed 990 grams. The infant developed moderate RDS and received rescue surfactant treatment. On day 3 of life, the infant developed a grade 3 intraventricular haemorrhage and neurogenic pulmonary oedema. He subsequently recovered, but developed post-

haemorrhagic hydrocephalus and mild bronchopulmonary dysplasia (BPD). A ventriculo-peritoneal shunt was planned. On day 80 of life the infant developed diarrhoea. His oral intake was withheld and a peripheral venous line was placed. The infant received broad-spectrum intravenous antibiotic coverage since the C-reactive protein level was 17 mg/ml. A blood culture was negative. During the night the electronic infusion pump alarmed, and the attending nurse noted that the infusion fluid chamber and infusion set were empty. She re-filled the chamber and then saw that the infant was quiet and cyanotic. On auscultation, a bradycardia was noted. Resuscitation commenced, but the infant could not be revived. Autopsy confirmed the presence of air within the right atrium and right ventricle. The lungs showed significant changes typical of BPD, but there was no evidence of extra-alveolar air.

Case 4

A premature female infant, weighing 1 020 g, developed significant anaemia by day 47 of life, despite medical treatment with subcutaneous erythropoietin and oral iron and vitamin E. On examination she was pale, but active. Her haematocrit was 25% and the corrected reticulocyte count 1.2%. Owing to the inadequate bone marrow response to erythropoietin treatment and the fact that she was about to be transferred to a rural hospital, a blood transfusion was planned. Before the transfusion a peripheral infusion catheter with a heparin lock was inserted. After ensuring that there was no air in the infusion set, the blood transfusion was started and controlled via a volume infusion pump. Approximately 90 minutes later, the attending physician went to check on the progress of the transfusion and discovered that the baby was lying motionless. Resuscitation was to no avail. Observations, including respiration, blood pressure and temperature, performed 30 minutes before the collapse of the infant, were normal. A postmortem chest radiograph performed within 30 minutes of the incident revealed the presence of intracardiac air. A forensic autopsy revealed the presence of air in the right ventricle.

Discussion

A devastating complication of neonatal intensive care is that of iatrogenic systemic air embolism, usually described in association with mechanical ventilation. Since 1969, and including the present study, more than 65 cases of systemic air embolism (AE) have been reported in newborn infants and infants below the age of 3 months. Of these, only 5 appear to have survived the neonatal period, 3 with severe neurological disability, 1 with an unreported outcome and 1 who died at the age of 7 months, following a viral pneumonia.[3-7] The infants described in the present study had a uniformly dismal outcome. Two of them were receiving assisted ventilation at the time of their clinical deterioration. In 1, a pneumothorax was considered to precede the final event; however, no extra-alveolar air could be demonstrated at autopsy. In all 4 of them, causality could be demonstrated between clinical deterioration and the events surrounding either the recent placement of a peripheral venous line, an infusion pump that alarmed, or an infusion set that ran 'dry'.

Mechanisms of air embolism

Several mechanisms have been proposed to explain the presence of air in the heart, brain and/or systemic vessels. The most popular explanation is that of pulmonary venous air embolism (PVE) occurring directly as a consequence of ventilator-induced barotrauma or the development of a bronchovenous fistula in the face of high intrabronchial pressures.[8-11] The majority of reported infants were receiving conventional mechanical ventilation and had roentgenographic evidence of a pre-existing air leak before developing the catastrophic AE.[9] However, vascular AE has been described as a complication of high-frequency ventilation and CPAP.[11,12] In the presence of pulmonary interstitial emphysema (PIE), it has been suggested that air within the pulmonary lymphatic system gains access to the systemic venous system via lymphatic ducts, resulting in neonatal systemic AE.[13] In the dog, iatrogenic over-expansion of the lung results in lung rupture at a level distal to the terminal bronchioles.[14] The air from this leak may enter the intrapleural space and/or may enter the pulmonary artery and/or veins. Haemodynamic changes include reversal of flow in the pulmonary artery and pulmonary and tricuspid incompetence.[14] A second, and less well recognised, mechanism of systemic air embolism is the introduction of air into the venous circulation via a peripheral site.[4,15] Whether receiving mechanical ventilation or not, air may be introduced into the venous circulation when peripheral infusion sets have been improperly prepared (inadequate flushing), an infusion set is allowed to run 'dry' or an infusion pump without pressure or air-sensing technology is used (case 3).[4,15] Air embolism has also been reported following a caesarean section. In this case it was speculated that air entered the cut lumen of the large veins and sinusoids as the placenta was incised.[16] Air may also accumulate after death.[17] A source of air may be the fluid bag itself. For instance, the 200 ml Neolyte bag (Intramed, South Africa) contains approximately 8 ml of air, whereas another commonly used fluid, glucose 5% and sodium chloride 0.2% (Adcock Ingram Critical Care Ltd) contains approximately 6 ml of air.

Physicians and nursing staff should be aware that very small amounts of intravenous air might cause significant AE in newborn infants. Most iatrogenic air emboli are venous in origin and isolated right-sided cardiac air is found significantly more often than air within the left chambers of the heart.[13] However, neonates are particularly vulnerable to developing

arterialisation of venous air since the foramen ovale (FO) may remain patent for an extended period after birth. This route could provide venous air with systemic access, especially in the face of raised pulmonary vascular pressures. In the newborn piglet, a total air dose of 2.5 ml (over 25 minutes) infused via the inferior vena cava, resulted in arterial (A) AE, without raising the pulmonary artery pressure.[18] In this model, gas bubbles were already detected within the left ventricle after only 45 seconds of infusion (0.01 ml/kg). These authors concluded that a right to left shunt over the FO exists during the first days of life in newborn piglets, even at normal pulmonary artery pressures, and that minute volumes of air can cause AAE.[18] A similar condition is present in the newborn infant who also experiences a significant right to left shunt across the FO, mainly as a consequence of a reverse sequence of valve opening, i.e. earlier opening of the mitral valve.[19] An air dose of 0.5 ml/kg/min produces cardiorespiratory instability, while 0.075 ml of air, injected directly into the anterior descending branch of the left coronary artery of the dog may cause death of the animal.[20,21]

Pathogenesis of air embolism

Trapped air causes neutrophil accumulation and activation in experimental animal models, with AE inducing acute lung injury to the microvasculature. Oxygen free radicals released by the activated neutrophils injure the pulmonary vascular endothelium. Subsequent increased permeability results in pulmonary oedema, release of thromboxane A_2, pulmonary vasoconstriction and increased vascular resistance and a tripled lung lymph flow.[22-25] The pathogenesis of the systemic changes induced by the arterialisation of air includes effects other than those observed due to the mechanical effects of bubbles arresting flow in certain parts of the circulation.[22,23,26,27]

Clinical symptoms and signs

Although two differing clinical pictures have been described for venous and arterial embolism in the adult animal or human, it may not be the case in the human newborn whose fetal channels may still be patent.[18,21] Immediately after air has entered the venous circulation, the presence of air in the right ventricle may be detected by a 'millwheel' murmur. In spontaneously breathing animals, tachycardia, tachypnoea, and cyanosis develop. Cyanosis becomes readily apparent as venous pressure rises and systemic blood pressure falls due to the air block of the right ventricle and right ventricular outflow tract.[21] These manifestations are also influenced by the body position. In AAE, the clinical picture is dependent upon ischaemia in vital organs, including the heart and brain.[21,28] Especially of note, is the observation of paleness or blanching or a marbled appearance of the skin of the right upper arm and right anterolateral chest wall.[3,21,28] This picture is caused by AAE to the axillary artery. The generalised mottling of the body that follows this event indicates that systemic arterial embolism has occurred. Systemic air embolism should be suspected when Liebermeister's sign is observed.[28] This sign describes areas of pallor on the tongue which may be focal, i.e. the edge of the tongue to the right of the tip, or more widespread, involving the right half of the tongue. This sign is not mentioned in any of the articles concerning air embolism published in the English literature, indicating that very few physicians are aware of its occurrence and possible diagnostic importance.

Coronary arteries are frequently involved in air embolism originating in the pulmonary circulation.[29] When bronchovenous fistulas were produced by raising intratracheal pressure in guinea pigs, convulsions and death followed within 50 - 75 seconds.[29] In these animals, autopsy revealed air in the coronaries. Right ventricular myocardial ischaemia is thought to result from a decrease in blood flow through the thebesian channels due to an increase in right ventricular pressure, in the presence of air, and a simultaneous drop in aortic pressure.[21] Electrocardiographic changes during neonatal systemic air embolism have not been well documented. In closed-thorax dog experiments, venous air embolism causes marked depression of S-T segments in standard leads II and III, rhythm disturbances, varying degrees of A-V block or the development of nodal rhythm. In surviving animals, the deviation of the S-T segments disappeared during recovery from the embolic disturbance.[21] The electrocardiographic changes observed during AEE in dogs are identical to those observed in instances of ischaemia induced by other means, i.e. vasospasm or obstruction.[28] AEE of the coronary arteries is characterised by varying electrocardiographic changes. These include T-wave changes, large Q-waves or broad QRS complexes due to an intraventricular block, a bigeminal rhythm or electrical alternans.[28]

The clinical consequence of cerebral arterial air embolism (CAAE) has not been well documented in the human newborn infant. Furthermore, there are only three references in the literature to cranial ultrasonography findings of cerebral vascular air embolism in the newborn infant.[3,30,31] This may be due partly to the catastrophic outcome described in the vast majority of these infants, a lack of clinical symptoms in an already compromised infant that would further raise the suspicion of central nervous system involvement, or a failure to recognise the diagnostic value of cranial ultrasonography during the acute phase of embolism. Pulsed Doppler examination of the anterior cerebral artery and other intracranial arteries has revealed the presence of a stream of bubbles, accompanied by a loss of Doppler flow signals.[31] An echogenic density, associated with an acoustic shadow with no through transmission, has been described once before, and now again in our present case 1 (Fig. 2).[3] The microscopic consequence of CAAE has been documented in experimental animals.[32,33] Much of the brain dysfunction that follows CAAE

may be due to effects that air has on vascular endothelial cells, such as vasoconstriction of the pial-arachnoidal microvessels, and not to the effects of bubble entrapment.[27,33] In adult rabbits diminished cortical somatosensory-evoked response after air embolism indicates impairment of the sensorimotor cortical function. This impairment correlated with a post-transit, gas-induced reduction in cerebral blood flow that lasted for up to 2 hours.[27] Although neurological injury after CAAE is dose-dependent, somatosensory-evoked potential abnormalities and neurological dysfunction (drowsiness, depressed reflexes) during microscopic CAAE appear not to be accompanied by cerebral infarction within 24 hours of the incident.[32] Without the sophisticated technology mentioned above, it is clear that the detection of subtle neurological abnormalities in already compromised infants would be very difficult, if not impossible.

Pyrogenic or other toxic substance contaminating infusion sets

Endotoxin, also referred to as lipopolysaccharide (LPS), and other peptides, released by Gram-negative bacteria, have been suggested as a possible causative mechanism in the collapse of the infants described above. Endotoxin is a potent modulator of the immune system and LPS-induced mononuclear cell activation results in excessive proinflammatory cytokine activation followed by fever and changes in haemodynamic variables, usually manifesting after 30 minutes, and in a dose-dependent manner.[34,35]

Pyrogen detection in parenteral pharmaceuticals remains problematic. For instance, the Limulus amoebocyte lysate test detects only LPS and false-negative test results have been reported.[36] Recently, a nursery outbreak of fever and clinical sepsis was followed by the death of 36 neonates in a single neonatal unit in Brazil.[37] A turbidimetric limulus amoebocyte lysate assay of intravenous fluids and medications identified high levels of endotoxin in bi-distilled water, suggesting that contamination via these vials could have been the cause of death in some, if not all, of these infants.

Although no special investigations were performed on the infusion sets or intravenous fluid to detect the presence of endotoxin as a possible causative factor for the infants' death in the present study, endotoxic shock appears to be unlikely. One could argue that in cases 2 and 4 endotoxic shock did contribute to the overall picture of collapse, but then one needs to explain the antemortem-detected intracardiac air in case 2 and the immediate postmortem radiographic and autopsy-confirmed air in case 4. It appears likely that systemic infection contributed to the overall picture in case 2. However, there are no reports in the English literature in which the presence of intravascular and intracardiac air have been linked to organisms causing gas formation during septicaemia. The postmortem accumulation of intravascular, intraperitoneal and cerebrovascular air has been described in 4 infants with respiratory distress syndrome.[17] Quisling and co-workers[17] suggested that physiological postmortem gas accumulates rapidly, i.e. within 25 minutes after death. Since this gas accumulation was progressive over the next 4 hours, the authors questioned the significance of postmortem gas unless the time between death and filming or postmortem interval is known. However, as pointed out, postmortem intracardiac air was an infrequent finding, only described in 1 of their 4 infants. In agreement with other studies of rapid air accumulation (embolism), we describe gas (air) within the right heart chambers, whereas gas distribution in the series by Quisling *et al*.[17] appeared to be venous in location, i.e. in the mesenteric, portal, hepatic and deep cerebral veins.

Could the presence of another toxic substance in infusion sets explain the acute clinical course of the 4 infants? It is known that containers made of polyvinylchloride (PVC) are able to leach plasticisers, especially diethylhexylphtalate (DEHP).[38] Furthermore, the amount of DHEP extraction by PVC lines is highly correlated with temperature, i.e. increases with increasing temperatures, and differing contents of infused lipids. Although the significance of high concentrations of DHEP is still debated, it has been associated with subacute and chronic hepatobiliary dysfunction and unexplained chronic lung disease in neonates, rather than with acute toxicity.[38]

Management of neonatal air embolism

The only way to treat air embolism is to prevent its occurrence. Drip sets and fluid bags should be appropriately de-aired, whereafter care should be taken to avoid the introduction of air into the closed system. A common practice is to catheterise the umbilical vein for purposes of resuscitation and administration of maintenance fluids during the early neonatal period. Although health professionals should be aware of the dangers of connecting a syringe to a vessel directly entering the heart in a child with potential right to left shunting, standards might be lower in less sophisticated units. The transfusion of blood through an additional length of tubing and connections that need to be primed represent other risks of air entrapment. Health care workers should avoid running fluid in under pressure unless required. Where fluid bags have not been rid of air it is theoretically possible that air could be infused into a patient via an electronic infusion pump if the bag and infusion set are allowed to run 'dry'.

When faced with an acute venous embolism, the resuscitation management of these infants should include prompt 'cardiopulmonary resuscitation'. Although this term is relatively non-descriptive, the majority of authors describe initiating artificial ventilation and cardiac massage, even if the infants were already receiving artificial ventilation, the use of vasopressors and/or volume expanders and the use of

bicarbonate and/or calcium chloride.[3,4,9,30] There is, however, no consensus on the optimal management of these infants and from the reported poor survival rates it is concluded that infants who 'collapse' following systemic air embolism are usually unresponsive to conventional resuscitation. Few physicians probably relate vascular air embolism to sudden collapse, and even fewer would consider turning a collapsed patient to the left lateral prone position with the head in slight Trendelenburg (body tilted downward from supine) to prevent air from entering the coronary arteries.[3] Nevertheless, work in animals has clearly shown that the left lateral position favours recovery, while the right lateral position is by far the worst for the animal.[21] With the animal on the side, the right ventricular outflow tract assumes a position inferior to the body of the right ventricle. Air, blocking the outflow tract, then disappears from this inferior position, is presumably mixed with blood in the right ventricular cavity and then expelled into the lungs via the pulmonary artery. Although the position of the body may be less important therapeutically in arterial embolism than in the pulmonary form, the head-down position may still prevent cerebral involvement.[21] The value of the capnograph as a sensitive monitor of air embolism during the assessment of the patency of ventriculo-cardiac shunts has been described.[39] In the referred study, the capnograph registered a fall in the expired CO_2 that preceded any change in blood pressure or other variable.

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