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CASE REPORT

Non-invasive ventilation for severe TRALI and myocardial stunning: report and literature review

M. Piastra · E. Luca · E. Stival · F. Caliandro · G. De Rosa · F. Giona · D. De Luca · G. Conti · D. Pietrini

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Abstract Transfusion-related acute lung injury (TRALI) is a frequently under-diagnosed, although potentially fatal, condition that represents a leading cause of transfusion-related morbidity and mortality even in pediatric patients. Its main clinical features are characterized by rapidly evolving respiratory distress, hypoxia, pulmonary edema, and bilateral infiltrates on chest radiograph during or within 6 h of transfusion. We present a case of severe TRALI associated with myocardial stunning that occurred in a 14-year-old girl, and review the existing literature of pediatric TRALI. Our report suggests a potential role for NIV in the management of TRALI as the best profile both in terms of safety and effectiveness for hematologic patients.

Keywords ALI · TRALI · TACO · Non-invasive ventilation · Hemotransfusion complications

M. Piastra · E. Luca (✉) · E. Stival · D. De Luca · G. Conti · D. Pietrini
Pediatric Intensive Care Unit, Emergency Department, Catholic University "A. Gemelli" Hospital, L. go Gemelli 8, 00168 Rome, Italy
e-mail: ersilialuca@hotmail.it

F. Caliandro
Cardiothoracic Intensive Care, St Georges Hospital NHS, London, UK

G. De Rosa
Pediatric Cardiology, Department of Paediatrics, Catholic University "A. Gemelli" Hospital, Rome, Italy

F. Giona
Department of Hematology and Cellular Biotechnologies, "La Sapienza" University, Rome, Italy

Introduction

Transfusion-related acute lung injury (TRALI) is a serious life-threatening condition often under diagnosed, representing a major cause of transfusion-related morbidity and mortality in pediatrics [1, 2]. Main clinical features are characterized by the rapid evolution of respiratory distress, hypoxia, pulmonary edema and bilateral infiltrates on chest radiograph during or within 6 h of transfusion [3].

Differential diagnosis includes allergic/anaphylactic reactions, transfusion-associated circulatory syndrome (TACO), bacterial contamination and hemolytic transfusion reactions [4]. Recent studies confirm an increased susceptibility to TRALI of critically ill patients (5.1–8 %), especially if mechanical ventilation is necessary [5].

Therapeutic approach involves non-disease-specific techniques, including oxygen supplementation, artificial ventilation and hemodynamic support. Ventilation itself can induce/sustain lung injury (high pressures) aggravating pulmonary and systemic course of TRALI [6]. We present one severe TRALI case suffering from severe hypoxemic respiratory failure treated in a Pediatric Intensive Care Unit (PICU), introducing non-invasive ventilation (NIV) as alternative to controlled mechanical ventilation (CMV).

Illustrative case

A 14-year-old female [body weight (BW) 38 kg] was affected by acute myeloid leukemia (AML) (M4 phenotype), in clinical remission after re-induction therapy (FLAG protocol [7]). Seven days later, a red blood cell (RBC) transfusion was needed (10 mL/kg of filtered packed RBC; 1 mL/kg/h) because of refractory epistaxis and severe anaemia (Hb 4.9 g/dL). The patient—apyretic

and stable prior to transfusion—developed fever (39.2 °C) and hypotension [systemic blood pressure (SBP) 70/40 mmHg] within 2 h from transfusion introduction. Shortly after, she presented a worsening respiratory distress with tachypnea [respiratory rate (RR) 50/min] and tachycardia [heart rate (HR) 135/min] and moderate hypoxia requiring mask oxygen support. Hemo-transfusion was discontinued when $SatO_2$ on room air suddenly dropped to 60 %. Her previous medical history was negative for any cardiac involvement, as 2D-Echo assessments. On PICU admission, her clinical status was poor: she appeared pale and diaphoretic, with signs of impending respiratory fatigue. Arterial blood gases (ABG) analysis at FiO_2 0.21 showed: pH 7.22; pO_2 54.9 mmHg; pCO_2 45 mmHg; HCO_3 18.4 mmol/L, Lactate (Lac) 5 mmol (PaO_2/FiO_2 148). She received electively NIV through a Helmet interface, maximizing patient-ventilator interaction [pressure support (PS) mode, flow-triggered, PS/positive end expiratory pressure (PEEP) 10:7]. Within 6 h, respiratory status was stabilized (FiO_2 0.28–0.30, HR 110/min, RR 25/min), ABG showed pH 7.36, pO_2 76 mmHg, pCO_2 32 mmHg, HCO_3 15.1 mmol/L, Lac 2.3 mmol (PaO_2/FiO_2 253).

A transfusion reaction was suspected and put in the differential diagnosis with TRALI, TACO and septic or acute hemolytic transfusion reaction. Chest X-rays (previously normal) revealed bilateral and diffuse pulmonary opacities without enlarged cardiac shadow, while a subsequent chest CT showed a bilateral alveolar-interstitial involvement, pleural effusion, multiple pulmonary lesions and bilateral atelectasis (Fig. 1). A 2D-echocardiography evidenced a marked heart dysfunction: severe hypo-contractility, ejection fraction (EF) 12 %, no left ventricle (LV) enlargement or mitral regurgitation (MR). Both brain natriuretic peptide (BNP) and Troponin T (TnT) values were within limits (<250 pg/ml and <0.1 pg/mL, respectively). Hemo-dynamics and pulmonary vascular permeability were assessed using trans-pulmonary thermodilution method [pulse contour continuous cardiac output (PiCCO), PULSION Medical Systems], permitting continuous cardiac output monitoring. Extra-vascular lung water index (EVLWI) and intrathoracic blood volume index (ITVBI) were also obtained. Central venous pressure (CVP) was 8 cmH_2O on PICU admission, whereas other preload indicators excluded circulatory overload (ITVBI <700/m^2), thereby making TACO diagnosis unlikely. Before hemodynamic support, Cardiac Index (CI) was 1.9 (Fig. 1), increasing with dobutamine (7.5–10 mcg/kg/min). Urine, blood, and cerebrospinal fluid cultures were negative. NIV was maintained for 3 days, and then shifted to continuous positive airway pressure (CPAP). Cardiac function recovered over 96 h; subsequent 2D-Echo assessments revealed a good contractility (stable EF >60 %). She was discharged after 9 days from PICU admission in good clinical conditions. Subsequent heart function evaluations showed a LV normal contractility, thus suggesting the diagnosis of transient heart stunning in association with a confirmed TRALI episode.

Discussion

Over the last decades, TRALI has emerged as one of the most important adverse effects of blood transfusions with considerable morbidity and mortality [8]. The statement from the TRALI Consensus Conference Committee describes acute onset acute lung injury (ALI), during or within 6 h of a transfusion, with no temporal relationship with an alternative ALI risk factor [9].

Acute onset lung injury is defined as appearance of bilateral infiltrates on frontal chest radiograph with no evidence of left atrial hypertension, and hypoxemia ($PaO_2/FiO_2 \leq 300$), or $SatO_2$ <90 % on room air. TRALI severity depends upon the susceptibility to develop a clinically significant reaction due to underlying disease, and upon the nature of triggers in the transfused blood components, including granulocyte-binding alloantibodies (immune TRALI)[10–12]. TRALI itself may occur as result of 2 events (''two-hit hypothesis''): the first one is the clinical condition (such as surgery, infections or malignancy), with priming of the patient's neutrophils, the second one is represented by the transfusion of ''bioactive factors'' activating primed neutrophils within the lungs, eventually causing ALI (non-immune TRALI) [13]. Despite available data, patients at risk of TRALI are still not properly identified, while prevention and treatment suggestions have been variably reported [14]. Volemic overload may represent a confounding factor, since no single feature distinguishes TRALI from TACO [15]: presentation, fluid status, cardiac function (including BNP) and leukocyte antibody can suggest the diagnosis.

Most pediatric cases (Table 1) are dealing with chronic conditions with anemia, where the unexpected pulmonary symptoms could not be readily attributed to an alternate diagnosis. A greater risk for TRALI in hematological malignancies during induction treatment has been demonstrated [32]. Pulmonary edema in TRALI is a result of increased vascular permeability, rather than increased hydrostatic pressure as in TACO: increased BNP is highly predictive of cardiac dyspnea [33].

PICU management consists of supportive measures including gas exchange optimization and cardio-circulatory support, avoiding fluid overload [5, 34]. A protective ventilation strategy is highly recommended, minimizing further lung injury [35, 36].

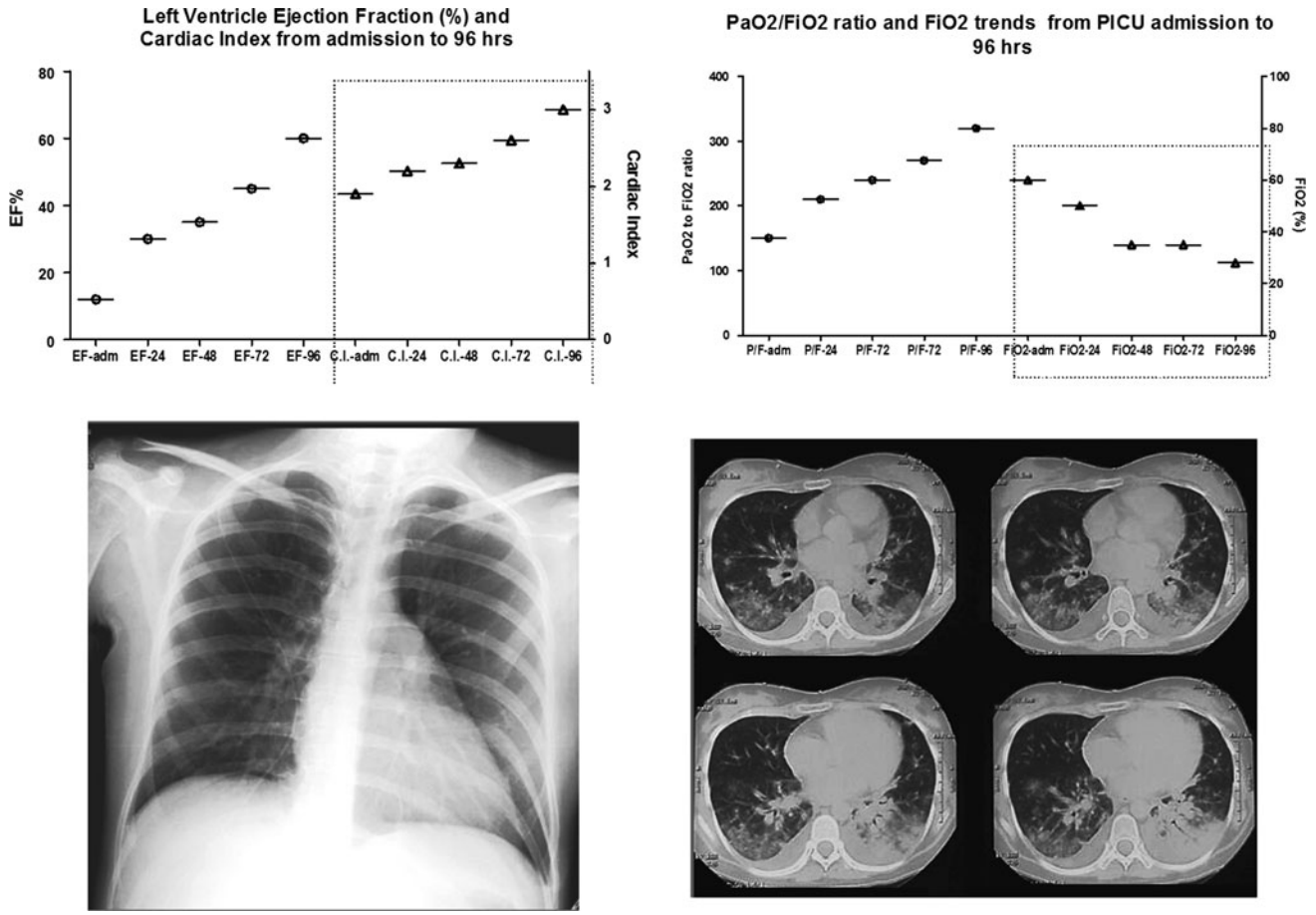

Fig. 1 Time course of cardiac function indicators (EF %, CI) and oxygenation parameters (PaO_2 to FiO_2 ratio, FiO_2) (UP) during the first 96 h PICU stay. Admission chest X-rays and chest CT scan of the patient showing dependent and basal lung opacities, in the absence of an enlarged cardiac shape

Cases of severe TRALI treated with NIV are not reported in pediatric literature (Table 1), paralleling the limited adoption of NIV techniques—even in hematologic patients—until recent years. Moreover, a role of CMV in TRALI pathogenesis has been hypothesized. Experimentally, Vlaar et al. [6] recently focused on the role of CMV, combining a murine model of ventilator-induced lung injury with a model of antibody-induced TRALI, confirming the causative role of invasive ventilation.

On the basis of an established treatment protocol for immune-depressed children, we electively adopted a NIV strategy, using a really comfortable interface. This treatment choice permitted to improve both oxygenation and lung recruitment over time, avoiding sedative agents and related hemodynamic depression. In fact, the coexistence of a transient myocardial stunning strongly advised against any hypotensive medication. Moreover, convincing data from the adult experience [37] as well as preliminary evidence in pediatrics suggested the superiority of NIV in terms of infectious complications [including ventilatory associated pneumonia (VAP) and septic shock] and shorter ICU stay. Recently, a further evidence from a randomized trial in adults seems to sustain very early NIV introduction, possibly preventing the evolution towards ALI [38]. However, we must not forget that such NIV approach should be offered in tertiary level centers only, where in case of NIV failure and/or scarce hemodynamic response, a prompt intervention by a PICU team could be offered, including advance techniques of vital organs support. In fact, in the unlikely event of failure of NIV and/or of a progression of the cardiac insufficiency, in this place we can provide for further assistance, such tracheal intubation and ECMO.

A diagnosis of acute myocardial stunning was made based on previous heart function and the absence of congestive heart failure (CHF). A careful revision of fluid balance before admission was made, excluding fluid overload or decreased urine output. As reported, both admission CVP and subsequent hemodynamic assessments permitted to rule out TACO as a possible causative mechanism. Heart function impairment lasted a few days with a progressive improvement and stabilized without any

Table 1 Reports of TRALI in pediatric literature (since 1972)

Age (years)/ sex	Diagnosis	D/A	PICU stay (days)	Blood product and indication for transfusion	Respiratory support	References
15/M	Hemophilia	A	3	Whole blood/FFP: anemia	O_2 therapy	Kernoff et al. [16]
9/M	Hemophilia	D	2	FFP: spontaneous hematoma	O_2 therapy	Kernoff et al. [16]
13/F	Thalassemia major	D	1	PRBC-anemia	O_2 therapy	Wolf and Canale [17]
3/F	Hemolytic disease of newborn	A	4	Bacterial sepsis following exchange transfusion	nd	O'Connor et al. [18]
1.3/M	Osteopetrosis	D	22	Thrombocytopenia pre-bone marrow biopsy	ETI + CMV	Madyastha et al. [19]
4.5/M	Osteopetrosis	D	1,5	PLTs/PRBC: surgery	ETI + CMV	Madyastha et al. [19]
0.1/M	Hyperbilirubinemia	A	–	Exchange transfusion	ETI + CMV + Surfactant	Wu et al. [20]
2.5/M	AML-autologous stem cell transplant	D	21	PLTs: thrombocytopenia	ETI + CMV	Leach et al. [21]
12/F	Ulcerative colitis	A	3	PRBC: surgery	ETI + CMV	Keifer et al. [22]
4/F	Cardiopathy	A	7	FFP cardiac surgery	ECMO + CMV	Nouraei et al. [23]
0.2/F	Cardiopathy	A	2	Cardiac surgery	ETI + CMV	Yang et al. [24]
0.1/M	Hemolytic disease of newborn	A	–	Exchange transfusion	nd	Gloster et al. [25]
0,2/M	Craniosynostosis	D	1	PRBC: surgery	ETI + CMV	Ririe et al. [26]
13/F	Thalassemia major	A	4	PRBC: anemia	ETI + CMV	Koussi et al. [27]
2/F	Down syndrome and AML	A	1	PLTs: thrombocytopenia	O_2 therapy	Lin Fung and Williams [28]
14/M	Acute promyelocytic leukemia	A	1	FFP: coagulopathy	O_2 therapy	Lin Fung and Williams [28]
13/F	Spondylolisthesis	A	3	PRBC/FFP: neurosurgery	ETI + CMV	Church et al. [29]
7/F	Liver tumor	A	–	PRBC: surgery	ETI + CMV	Church et al. [29]
0,6/F	Hydrocephalus and ventriculoperitoneal shunt	D	1	PRBC: anemia	ETI + CMV	Yildirim et al. [30]
8/M	Hemophilia (F VIII 10 %)	A	10	FFP: right perirenal hematoma	O_2 therapy	Yildirim et al. [30]
10/M	Aplastic Anemia	D	1	PRBC: anemia	ETI + CMV	Sharma et al. [31]

AML acute myeloid leukemia, *ECMO* extra-corporeal-membrane-oxygenation, *FFP* fresh frozen plasma, *ETI* endo-tracheal intubation, *PLTs* platelets, *PRBC* packed red blood cell, *CMV* controlled mechanical ventilation

recurrence: both 2D-Echocardiography and enzyme profile remained within limits over time.

Conclusion

Although the limited experience and the absence of any randomized controlled trial (RCT), the ICU management of a critically ill child with TRALI should include a lung protective strategy. NIV can offer the best profile both in terms of safety and effectiveness for hematologic patients. Early identification, timely NIV approach and careful hemodynamic monitoring should be warranted in complicated cases.

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