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Corticosteroid Responsiveness in Acute Respiratory Distress Syndrome of Different Aetiologies: A Two-Patient Case Series

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ABSTRACT

Introduction: Acute respiratory distress syndrome (ARDS) is a life-threatening, biologically heterogeneous form of acute hypoxaemic respiratory failure arising from a broad spectrum of direct and indirect pulmonary insults. Although lung-protective ventilation and supportive care remain the foundation of management, the role of corticosteroids is still debated, with benefit concentrated in carefully selected patients and specific inflammatory phenotypes. We describe two patients whose ARDS arose from distinct aetiologies yet responded favourably to low-dose corticosteroid therapy.

Case Presentation: The first patient was a 14-year-old girl with Marfan syndrome who developed abrupt severe hypoxaemia with bilateral infiltrates within six hours of massive intraoperative transfusion during scoliosis correction, consistent with post-transfusion (transfusion-related) acute lung injury. The second was a 39-year-old man with severe ARDS from bilateral pulmonary contusion after blunt chest trauma, complicated by *Acinetobacter baumannii* and *Enterobacteriaceae* hospital-acquired pneumonia. Both received lung-protective mechanical ventilation with individualised positive end-expiratory pressure and intravenous methylprednisolone 62.5 mg/day. Oxygenation and radiographic appearance improved progressively, with the ratio of arterial oxygen tension to inspired oxygen fraction rising from 72 to 343 by day 5 in the first patient and from 72 to 357 by day 11 in the second, permitting successful liberation from the ventilator.

Conclusion: In these two aetiologically distinct patients, early low-dose methylprednisolone added to lung-protective ventilation was associated with rapid clinical and radiographic recovery. The series supports an individualised, aetiology- and phenotype-aware approach to adjunctive corticosteroid therapy in ARDS rather than uniform application or avoidance.

1. Introduction

Acute respiratory distress syndrome (ARDS), first described more than five decades ago, is a severe form of acute lung injury defined by the acute onset of hypoxaemia, bilateral radiographic opacities, and non-cardiogenic pulmonary oedema. The 2024 global definition of ARDS reframed the syndrome around acute hypoxaemic respiratory failure with bilateral opacities not fully explained by cardiac failure or fluid overload, and deliberately broadened diagnostic recognition to include patients supported by high-flow nasal oxygen and resource-limited settings, while retaining the principle that severity is graded by the degree of oxygenation impairment.[1] Contemporary analyses applying this framework to large critical-care databases confirm that mortality continues to rise across ascending severity strata, with pooled estimates of approximately 35% in mild, 40% in moderate, and 46% in severe disease.[2] Despite decades of refinement in supportive care, ARDS

therefore remains a high-mortality condition that consumes a disproportionate share of intensive-care resources.

The historical trajectory of the syndrome's definition helps explain why its management has remained contested. The 1994 American-European Consensus Conference and the subsequent 2012 Berlin definition progressively standardised diagnostic criteria and introduced severity strata based on the ratio of arterial oxygen tension to inspired oxygen fraction, providing a common language for research and practice. The 2024 global definition extended this work by accommodating oxygen-saturation-based diagnosis and non-invasive respiratory support, thereby improving case ascertainment in settings where arterial blood-gas sampling or invasive ventilation may be delayed or unavailable.[1] Even so, the definitions describe a clinical picture rather than a mechanism, and it is the underlying mechanism, whether direct alveolar injury, indirect endothelial activation, or an immune-mediated permeability insult, that ultimately determines both prognosis and the likelihood of response to a given therapy. This gap between a syndromic definition and a mechanistic understanding is the conceptual space within which decisions about adjunctive corticosteroids are made.

A central and increasingly appreciated feature of ARDS is its heterogeneity. The syndrome is not a single disease but a common physiological endpoint reached through a wide spectrum of direct pulmonary injuries, such as pneumonia, aspiration, and pulmonary contusion, and indirect insults, such as non-pulmonary sepsis, major trauma, pancreatitis, and transfusion of blood products. This aetiological diversity is mirrored at the biological level by distinct inflammatory subphenotypes. Hyperinflammatory and hypoinflammatory subphenotypes differ in circulating biomarker profiles, clinical trajectory, and, critically, in their response to therapy; recent work demonstrates that these subphenotypes are temporally stable over the early course of illness and that their recognition carries direct implications for the timing and likely benefit of corticosteroid therapy.[3] The heterogeneity of ARDS thus provides both an explanation for the inconsistent results of interventional trials and a rationale for individualising treatment according to the precipitating cause and the inflammatory context.

Corticosteroids occupy an especially contested place in this landscape. Mechanistically, glucocorticoids attenuate the dysregulated systemic and pulmonary inflammation that drives alveolar-capillary barrier disruption, and they may limit the fibroproliferative response that characterises the later, non-resolving phase of the syndrome. Randomised evidence and aggregate syntheses suggest that, when used at low dose and initiated early, corticosteroids can reduce mortality, improve oxygenation, and increase ventilator-free days in selected ARDS populations.[4,5] Yet the same agents carry recognised hazards, including hyperglycaemia, potential for delayed pathogen clearance, and, at high dose, a signal towards harm; observational cohorts have reported increased mortality where high-dose regimens or confounding by indication predominate.[4] The net effect of corticosteroids therefore appears to be conditional rather than categorical, depending on dose, timing, the specific agent selected, and the biological substrate of the individual patient.

Certain patients present with vulnerabilities that further complicate this calculus. In connective-tissue disorders such as Marfan syndrome, abnormalities of fibrillin-1 and dysregulated transforming growth factor-beta signalling may amplify tissue inflammation and impair repair, while simultaneously raising concern about wound healing, skin integrity, and skeletal fragility during corticosteroid exposure.[6] In trauma patients, the combination of direct parenchymal injury and superimposed nosocomial infection can broaden the area of lung involvement and blur the boundary between inflammatory and infective drivers of hypoxaemia. These scenarios expose the limits of a uniform therapeutic policy and highlight the need for aetiology-aware clinical reasoning.

Here we report a case series of two patients who developed ARDS from clearly distinct aetiologies, namely post-transfusion acute lung injury in an adolescent with Marfan syndrome and trauma-related

ARDS from blunt-force pulmonary contusion complicated by multidrug-resistant nosocomial pneumonia, and who each demonstrated a favourable clinical and radiographic response to low-dose methylprednisolone added to lung-protective ventilation. The novelty of this report lies in the direct juxtaposition of two mechanistically dissimilar forms of ARDS that nonetheless converged on the same adjunctive therapy and a similar recovery trajectory, and in the illustration of how connective-tissue and infective comorbidities shape the risk-benefit assessment of steroids at the bedside. The aim of this study is to describe the clinical course, ventilatory and biochemical trajectory, and radiographic evolution of these two patients, and to situate their management within contemporary evidence, in order to argue for an individualised, phenotype- and aetiology-informed approach to corticosteroid use in ARDS.

2. Case Presentation

Case 1: Post-transfusion ARDS in an adolescent with Marfan syndrome

A 14-year-old girl with a body weight of 31 kg and a known diagnosis of Marfan syndrome was scheduled for posterior scoliosis correction for a severe dextroscoliosis with a Cobb angle of 93°. Her phenotype included arachnodactyly and trivial tricuspid regurgitation. She was assessed as American Society of Anesthesiologists (ASA) physical status III on the basis of the syndromic connective-tissue disorder and the magnitude of the planned spinal reconstruction. Preoperatively her condition was optimised, with no respiratory complaints, a clear chest radiograph, and unremarkable baseline laboratory results. Transthoracic echocardiography demonstrated preserved left ventricular systolic function with an ejection fraction of 61.2%, normal diastolic function with an E/A ratio of 1.7, and preserved right ventricular function with a tricuspid annular plane systolic excursion (TAPSE) of 1.9 cm. Dilatation of the aortic root and arch consistent with Marfan syndrome was noted, without evidence of left atrial enlargement. The principal baseline and admission parameters are summarised in Table 1.

The scoliosis correction proceeded over approximately four hours. Intraoperative blood loss was substantial, at approximately 2,900 mL, and was managed with a cumulative 1,800 mL of blood products comprising 800 mL of packed red cells, 700 mL of whole blood, and 300 mL of fresh frozen plasma. The patient was transferred to the intensive care unit (ICU) intubated and mechanically ventilated, with an initial set respiratory rate of 20 breaths/min, tidal volume 300 mL (approximately 9.7 mL/kg of actual body weight), pressure support 10 cmH_2O, inspired oxygen fraction (FiO_2) 40%, and positive end-expiratory pressure (PEEP) 10 cmH_2O. Admission investigations showed a haemoglobin of 11.7 g/dL, haematocrit 35.2%, mean corpuscular volume 86.9 fL, white-cell count 13,800/mm^3, and platelet count 86,000/mm^3. Renal indices were deranged, with urea 161 mg/dL and creatinine 4.9 mg/dL, and the serum lactate was elevated at 5.7 mmol/L with an albumin of 3.4 g/dL. Venous blood-gas and electrolyte analysis showed sodium 140 mEq/L, chloride 108 mEq/L, potassium 4.25 mEq/L, ionised-equivalent calcium 8.3 mg/dL, pH 7.31, bicarbonate 19.1 mmol/L, and a ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2) of 184 at the point of transfer.

Within approximately six hours of the transfusion episode, the patient deteriorated abruptly, developing hypotension, desaturation, and tachycardia that necessitated escalation of ventilatory support. Physical examination revealed bilateral pulmonary rhonchi on auscultation with rhythmic heart sounds, no murmurs or added sounds, and no peripheral oedema. Chest radiography now demonstrated bilateral infiltrates across both lung fields where the immediately preceding film had been comparatively clear. In the absence of any clinical or electrocardiographic evidence of cardiac failure or volume overload, and given the close temporal relationship to the administration of blood products, the deterioration was attributed to post-transfusion acute respiratory distress, that is, transfusion-related acute lung injury. The nadir PaO_2/FiO_2 during this phase fell to 72, placing the patient in the severe ARDS category. The serial radiographic evolution during the ICU course is shown in Figure 1.

Table 1. Baseline demographic, clinical, laboratory, and echocardiographic parameters of Case 1 at ICU admission.		
Parameter	**Value**	**Reference / remark**
Demographic and surgical profile		
Age / gender	14 years / female	Adolescent
Body weight	31 kg	Low body mass for age
Underlying diagnosis	Marfan syndrome	Arachnodactyly; trivial tricuspid regurgitation
Deformity	Dextroscoliosis, Cobb angle 93°	Severe curve
Procedure	Posterior scoliosis correction (~4 h)	ASA physical status III
Intraoperative blood loss	~2,900 mL	Massive haemorrhage
Blood products transfused	1,800 mL (PRC 800 / whole blood 700 / FFP 300)	Massive transfusion context
Haematology and biochemistry		
Haemoglobin	11.7 g/dL	Post-resuscitation
Haematocrit	35.2 %	-
Mean corpuscular volume	86.9 fL	Normocytic
White-cell count	**13,800 /mm³**	Leucocytosis
Platelet count	**86,000 /mm³**	Thrombocytopenia
Urea	**161 mg/dL**	Markedly elevated
Creatinine	**4.9 mg/dL**	Acute kidney injury
Serum lactate	**5.7 mmol/L**	Hyperlactataemia
Albumin	3.4 g/dL	Mild hypoalbuminaemia
Sodium / Chloride / Potassium	140 / 108 / 4.25 mEq/L	Within range
Calcium	8.3 mg/dL	Low-normal
pH / HCO_3^-	**7.31 / 19.1 mmol/L**	Metabolic acidosis
PaO_2/FiO_2 at transfer	184	Moderate impairment at ICU transfer
Echocardiography		
Left ventricular ejection fraction	61.2 %	Preserved systolic function
E/A ratio	1.7	Normal diastolic relaxation
TAPSE	1.9 cm	Preserved RV function
Aortic root and arch	Dilated	Consistent with Marfan syndrome

Notes: ASA, American Society of Anesthesiologists; ICU, intensive care unit; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; MCV, mean corpuscular volume; AKI, acute kidney injury.

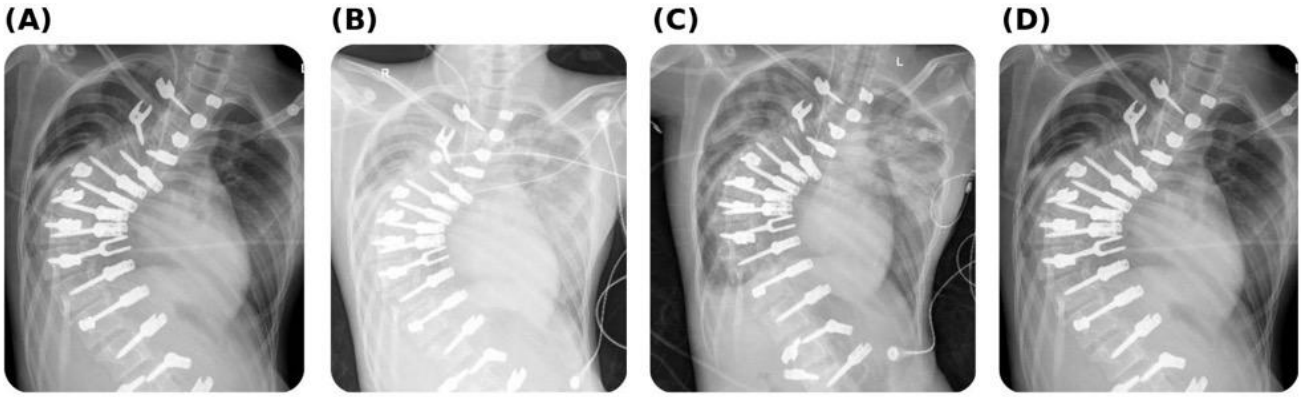

Figure 1. Serial anteroposterior chest radiographs of Case 1 during the intensive-care course, showing the posterior spinal instrumentation from scoliosis correction. (A) At the onset of post-transfusion acute respiratory distress with dense bilateral infiltrates (PaO_2/FiO_2 72). (B) Early post-onset film with partial clearing (PaO_2/FiO_2 134). (C) Intensive-care day 3 with further resolution (PaO_2/FiO_2 180). (D) Intensive-care day 5 with near-complete clearing of the infiltrates (PaO_2/FiO_2 343). Laterality markers (R, L) are the only annotations; no patient-identifying information is present.

Several concurrent derangements framed the therapeutic decisions at this point. The patient was thrombocytopenic and had biochemical evidence of acute kidney injury with a creatinine of 4.9 mg/dL and a urea of 161 mg/dL, together with a metabolic acidosis and hyperlactataemia that reflected the magnitude of the intraoperative haemorrhage and resuscitation. These findings were relevant to the choice of a low, fixed corticosteroid dose rather than a high-dose regimen, because they signalled a patient with limited physiological reserve in whom the metabolic and immunological costs of aggressive immunosuppression would be least well tolerated. Fluid administration was managed conservatively to avoid compounding the permeability oedema, while renal function and acid-base status were monitored closely and supported. The abrupt, transfusion-associated onset of hypoxaemia against this background was the decisive feature pointing to a transfusion-related, inflammatory mechanism rather than to hydrostatic pulmonary oedema.

Management centred on lung-protective mechanical ventilation with a low tidal volume, individualised PEEP, and conservative fluid handling, together with low-dose intravenous methylprednisolone at 62.5 mg per 24 hours as an adjunctive anti-inflammatory measure. The response was rapid and sustained. As detailed in Table 2, the PaO_2/FiO_2 ratio improved progressively from a nadir of 72 at the onset of injury (Figure 1A) to 134 shortly thereafter (Figure 1B), 180 by ICU day 3 (Figure 1C), and 343 by ICU day 5 (Figure 1D). In parallel, the serum lactate fell from 5.7 to 2.2, 1.0, and 1.3 mmol/L across the same timepoints, and PEEP was weaned from 10 to 6 cmH_2O as oxygenation recovered. The radiographs mirrored this trajectory, with progressive clearing of the bilateral infiltrates against the background of the posterior spinal instrumentation. The patient made a full clinical recovery and was liberated from mechanical ventilation.

Table 2. Serial ventilatory, oxygenation, and metabolic trajectory of Case 1 during the ICU course (corresponding to Figure 1A-D).

Timepoint	PEEP (cmH_2O)	Serum lactate (mmol/L)	PaO_2/FiO_2	ARDS severity
ARDS onset (Figure 1A)	10	5.7	**72**	Severe
Early post-onset (Figure 1B)	10	2.2	134	Moderate
ICU day 3 (Figure 1C)	10	1.0	180	Moderate
ICU day 5 (Figure 1D)	6	1.3	343	Resolved / mild

Notes: Timepoints correspond to the serial radiographs shown in Figure 1A-D. PEEP, positive end-expiratory pressure; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; ARDS severity graded according to the Berlin criteria.

Case 2: Trauma-related ARDS from pulmonary contusion

The second patient was a 39-year-old man admitted to the ICU with acute respiratory distress syndrome following blunt chest trauma sustained in an assault. He had been intubated in the emergency department because of a depressed level of consciousness, with a Glasgow Coma Scale score of 7 out of 15. Initial chest imaging demonstrated pulmonary contusion without accompanying thoracic skeletal fractures. During the ICU course he developed progressive hypoxaemic respiratory failure requiring invasive mechanical ventilation, with arterial blood-gas analysis documenting a nadir PaO_2/FiO_2 ratio as low as 72, with serial ratios remaining between 72 and 102 over the first three intensive-care days before recovery began, consistent with severe ARDS. His clinical summary and serial ventilatory and oxygenation trajectory are presented in Table 3.

Table 3. Clinical summary and serial oxygenation trajectory of Case 2 (corresponding to Figure 2A-D).		
Parameter / timepoint	**Value**	**Remark**
Clinical profile		
Age / gender	39 years / male	Adult
Mechanism	Blunt chest trauma (assault)	Direct pulmonary injury
Presenting GCS	7 / 15	Intubated in emergency department
Initial imaging	Pulmonary contusion, no bony fracture	Direct parenchymal injury
Nadir PaO_2/FiO_2	**72 (range 72-102)**	Severe ARDS
Radiographic pattern	Bilateral infiltrates + left pleural effusion	Contusion + HAP
Microbiology (sputum)	*Acinetobacter baumannii* + *Enterobacteriaceae*	Blood cultures negative
Adjunctive therapy	Methylprednisolone 62.5 mg/day	After antimicrobial cover
Serial oxygenation and support		
ICU day 1 (Figure 2A)	PEEP 14 cmH_2O; PaO_2/FiO_2 72	Severe
ICU day 4 (Figure 2B)	PEEP 14 cmH_2O; PaO_2/FiO_2 134	Moderate
ICU day 9 (Figure 2C)	PEEP 10 cmH_2O; PaO_2/FiO_2 176	Moderate
ICU day 11 (Figure 2D)	NRBM 10 L/min; PaO_2/FiO_2 357	Weaned from ventilator

Notes: Timepoints correspond to the serial radiographs shown in Figure 2A-D. GCS, Glasgow Coma Scale; ICU, intensive care unit; PEEP, positive end-expiratory pressure; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; MDR, multidrug-resistant.

Serial chest radiographs showed persistent bilateral pulmonary infiltrates with a left-sided pleural effusion, a pattern consistent with pulmonary contusion complicated by hospital-acquired pneumonia. Sputum cultures grew *Acinetobacter baumannii* together with *Enterobacteriaceae*, both reported as susceptible to the broad-spectrum antimicrobial agents employed, while blood cultures remained negative. Management therefore combined lung-protective mechanical ventilation with targeted antimicrobial therapy directed at the identified organisms. Adjunctive corticosteroid therapy with intravenous methylprednisolone 62.5 mg/day was initiated once the inflammatory, rather than purely infective, contribution to the hypoxaemia was judged to predominate and appropriate antimicrobial cover was in place. As shown in Figure 2, oxygenation improved steadily over the ensuing days, with the PaO_2/FiO_2 ratio rising from 72 on the first ICU day (Figure 2A) to 134 by day 4 (Figure 2B), 176 by day 9 (Figure 2C), and approximately 357 by day 11 (Figure 2D), at which point the patient had been weaned from invasive ventilation to a non-rebreathing mask at 10 L/min. Radiographic stabilisation and overall clinical recovery accompanied the improvement in gas exchange over roughly seven days of intensive care.

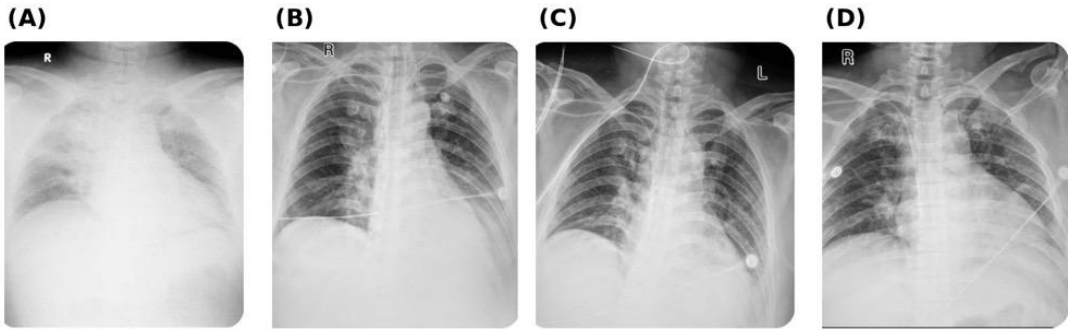

Figure 2. Serial anteroposterior chest radiographs of Case 2 following blunt-trauma pulmonary contusion complicated by hospital-acquired pneumonia. (A) Intensive-care day 1 with extensive bilateral opacification and near white-out (PaO_2/FiO_2 72). (B) Day 4 with substantial aeration recovery (PaO_2/FiO_2 134). (C) Day 9 with further clearing and residual basal changes (PaO_2/FiO_2 176). (D) Day 11 with largely clear lung fields after liberation from invasive ventilation (PaO_2/FiO_2 357). Only anatomical laterality markers are shown; the images carry no personal identifiers.

3. Discussion

These two patients illustrate a recurring clinical dilemma: ARDS presenting through entirely different aetiological routes, yet each responding favourably to the same adjunctive strategy of low-dose methylprednisolone layered upon lung-protective ventilation. Although the 2024 global definition of ARDS provides unified diagnostic criteria centred on acute bilateral radiographic opacities and hypoxaemia not explained by cardiac failure, the syndrome is more usefully understood as a complex, multifactorial process than as a single disease.[1] The shared pathophysiology involves dysregulated systemic inflammation, increased permeability of the endothelial and epithelial barriers, and diffuse alveolar injury, culminating in alveolar oedema that may, in a subset of patients, progress to fibrosis, necrosis, and proteinosis. The classical pathological evolution follows three partially overlapping phases, exudative, proliferative, and fibrotic, yet not every patient traverses every phase, and the stages do not always develop in a uniform or sequential manner.[2] This variability in trajectory is precisely what makes both prognostication and the timing of adjunctive therapy so difficult.

A comparative overview of the two cases is presented in Table 4, which juxtaposes their aetiology, presumed dominant mechanism, comorbid modifiers, ventilatory strategy, corticosteroid rationale, and response. The value of placing the two patients side by side lies in what their differences reveal: the first patient represents an indirect, immune-mediated insult superimposed on a connective-tissue disorder, whereas the second represents a direct parenchymal injury compounded by nosocomial infection. That both improved on comparable regimens does not prove that corticosteroids were decisive in either instance, but it does demonstrate that a single, mechanistically plausible adjunct can be rational across a spectrum of ARDS aetiologies when it is applied thoughtfully and at an appropriate dose.

Table 4. Comparative synthesis of the two aetiologically distinct ARDS presentations.

Feature	Case 1	Case 2
Age / gender	14 y / female	39 y / male
Aetiology of ARDS	Post-transfusion (TRALI-type) lung injury	Blunt-trauma pulmonary contusion
Injury pathway	Indirect, immune-mediated	Direct parenchymal injury
Dominant mechanism	Transfusion-primed inflammatory permeability oedema	Contusional inflammation + nosocomial infection
Key comorbid modifier	Marfan syndrome (fibrillin-1 / TGF-beta; aortic dilatation)	MDR *Acinetobacter* + *Enterobacteriaceae* HAP
Ventilatory strategy	Low tidal volume; PEEP 10 to 6 cmH_2O	Low tidal volume; PEEP 14 to 10 cmH_2O
Corticosteroid	Methylprednisolone 62.5 mg/day, early	Methylprednisolone 62.5 mg/day, post-antibiotics
PaO_2/FiO_2 (nadir to recovery)	72 to 343	72 to 357
Time to recovery	~5 days	~7-11 days
Outcome	Full recovery; ventilator liberation	Recovery; weaned to non-rebreathing mask

Notes: TRALI, transfusion-related acute lung injury; ARDS, acute respiratory distress syndrome; TGF-beta, transforming growth factor-beta; PEEP, positive end-expiratory pressure; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; MDR, multidrug-resistant; HAP, hospital-acquired pneumonia.

The heterogeneity of ARDS and the rationale for individualised therapy

The recognition that ARDS comprises biologically distinct subphenotypes has transformed the interpretation of interventional trials. Hyperinflammatory and hypoinflammatory subphenotypes, distinguished by circulating inflammatory markers and by clinical and physiological variables, exhibit different mortality and, importantly, different responses to a range of interventions. Recent evidence that these subphenotypes remain temporally stable across the early days of critical illness strengthens the argument that phenotype can inform, rather than merely describe, treatment, and it specifically identifies early corticosteroid therapy as an intervention whose benefit is likely to be concentrated in the more inflammatory patients.[3] Framed this way, the persistent controversy over corticosteroids in ARDS is less a contradiction than a reflection of averaging heterogeneous responders and non-responders within single trial populations. The two patients reported here can be understood in this light: each had a strong inflammatory driver, transfusion-triggered immune activation in the first and contusion-plus-infection-driven cytokine release in the second, that provided a coherent biological target for anti-inflammatory therapy.

This interpretation is consistent with the direction of the most recent aggregate evidence. A meta-analysis of corticosteroids in ARDS reported that, within randomised trials, corticosteroids were associated with a reduction in mortality (relative risk approximately 0.80), with the benefit most evident for low-dose regimens and for methylprednisolone and dexamethasone specifically; the same synthesis cautioned that observational data and high-dose regimens pointed in the opposite direction, underscoring that dose and study design shape the apparent effect.[4] A broader systematic review and meta-analysis of corticosteroids across critically ill populations, incorporating forty-three randomised trials and more than ten thousand patients, found that corticosteroids reduced short-term mortality and duration of mechanical ventilation, increased ventilator-free days, and improved the oxygenation index, with the greatest benefit when therapy was initiated early, given at low dose, and continued for at least seven days.[5] The regimen used in both of our patients, methylprednisolone 62.5 mg/day begun early in the ICU course, aligns closely with this profile.

Choice of agent, dose, and timing

Beyond the decision to use corticosteroids at all, the choice of agent and dose is consequential. A network meta-analysis comparing corticosteroids, neuromuscular blocking agents, and inhaled nitric oxide in ARDS ranked methylprednisolone highest among the compared strategies for preventing ICU mortality, while dexamethasone ranked highest for increasing ventilator-free days, findings that support agent-specific rather than class-wide conclusions.[7] Direct randomised comparisons of equivalent doses of dexamethasone, methylprednisolone, and hydrocortisone in ARDS have likewise been undertaken, reflecting genuine clinical equipoise about the optimal molecule, and randomised data on distinct dexamethasone dosing regimens have examined their effect on ventilator-free days and longer-term mortality.[8,9] A randomised comparison of methylprednisolone pulse therapy against intravenous dexamethasone further illustrates that both the molecule and the dosing strategy influence outcome.[10] Methylprednisolone is frequently favoured in the context of parenchymal lung injury on pharmacological grounds, including relatively high glucocorticoid-receptor affinity, good penetration into lung tissue, and prolonged tissue retention, characteristics that make a low, non-pulse daily dose an attractive compromise between anti-inflammatory efficacy and systemic toxicity. Its intermediate duration of action permits steady suppression of the inflammatory cascade without the abrupt swings associated with high-dose pulse therapy, and its predictable pharmacokinetics facilitate a straightforward daily regimen that is easy to titrate and to taper. The dose selected in both patients, 62.5 mg per 24 hours, corresponds to a genuinely low daily exposure that sits well within the range associated with benefit rather than harm in randomised data, and it avoids the supraphysiological dosing that has

been linked, particularly in observational cohorts, to increased mortality and to complications such as neuromuscular weakness and hyperglycaemia. In both patients reported here, a fixed low dose of 62.5 mg/day was selected rather than a high-dose or pulse regimen, in keeping with the weight of evidence favouring lower doses.

The timing of initiation is equally important. The observation that benefit is greatest when corticosteroids are begun early, generally within seventy-two hours of ARDS onset, and that this benefit is concentrated in more inflammatory patients, provides a principled basis for the early introduction of methylprednisolone once the diagnosis was established in each case.[3,5] In the first patient, therapy was started promptly after the abrupt post-transfusion deterioration; in the second, it was introduced once the balance of hypoxaemic drivers was judged to favour inflammation over uncontrolled infection and adequate antimicrobial cover had been secured. The subsequent trajectories, with PaO_2/FiO_2 improving to 343 and 357 respectively and lactate normalising in the first patient, are consistent with, although they cannot by themselves prove, a beneficial pharmacological effect.

Aetiology 1: Transfusion-related acute lung injury and the Marfan substrate

The first patient's presentation is characteristic of transfusion-related acute lung injury (TRALI), a form of ARDS precipitated by the transfusion of blood products. The temporal signature was typical: abrupt hypoxaemia with new bilateral infiltrates developing within approximately six hours of a large transfusion burden, in the absence of clinical, radiographic, or electrocardiographic evidence of circulatory overload or cardiac failure. The principal alternative diagnosis, transfusion-associated circulatory overload, was considered less likely on the basis of the preserved biventricular function on echocardiography, the absence of clinical features of hydrostatic overload such as a raised jugular venous pressure or gallop rhythm, and the conservative fluid strategy employed; the distinction is clinically important because circulatory overload would call for diuresis rather than for the anti-inflammatory and lung-protective approach adopted here. TRALI is understood to arise from the interaction of recipient neutrophils primed by an underlying inflammatory state with mediators present in transfused products, leading to pulmonary endothelial injury and high-permeability oedema; the intensity of the inflammatory response, rather than simple hydrostatic overload, drives the lung injury, and adjunctive strategies that target this inflammatory cascade have been explored in critically ill patients with TRALI.[11] The magnitude of this patient's transfusion exposure, approximately 1,800 mL of mixed products administered against roughly 2,900 mL of surgical blood loss, is itself a recognised context for transfusion-associated pulmonary complications, and the ratio and composition of products transfused during massive resuscitation have been linked to divergent outcomes in bleeding patients.[12] Situated within this framework, the rapid response to anti-inflammatory therapy is mechanistically coherent, because the dominant lesion in TRALI is an inflammatory, permeability-type oedema rather than a fixed structural defect.

The transfusion itself deserves closer scrutiny, because massive transfusion is not a uniform exposure but a physiologically complex intervention whose composition influences outcome. This patient received a mixture of packed red cells, whole blood, and fresh frozen plasma to counter roughly 2,900 mL of blood loss during a prolonged spinal reconstruction. Contemporary trauma-resuscitation data indicate that the ratio of platelets and plasma to red cells materially affects outcomes in patients requiring massive transfusion, and that both under- and over-resuscitation with particular components carry distinct risks.[12] In the context of a permeability-type lung injury, each plasma-containing product also delivers a potential inflammatory and antibody load capable of priming or activating pulmonary neutrophils, which is the pathophysiological substrate of transfusion-related lung injury. The clinical lesson is that transfusion strategy during major surgery is not merely a haemostatic calculation but also a determinant of pulmonary risk, and that a high index of suspicion for transfusion-related lung injury should follow any large or mixed-product

transfusion, especially when hypoxaemia appears within the classic six-hour window and cardiac causes have been excluded.

The Marfan syndrome background adds a further dimension. In Marfan syndrome, mutations affecting fibrillin-1 lead to dysregulation of transforming growth factor-beta signalling, a pathway increasingly delineated in mechanistic studies of the disorder and its vascular complications, and one that may amplify inflammatory responses and predispose to abnormal tissue remodelling.[6] The cardiovascular fragility that accompanies the syndrome, including aortic root and arch dilatation of the kind demonstrated on this patient's echocardiography, and the broader spectrum of arterial events that distinguishes Marfan syndrome from related heritable connective-tissue disorders, means that the physiological reserve available to withstand a severe hypoxaemic insult may be diminished.[13] Consequently, the development and progression of ARDS in a patient with Marfan syndrome cannot be attributed solely to increased alveolar-capillary permeability; it may also reflect the combined influence of connective-tissue fragility, growth-factor dysregulation, and haemodynamic vulnerability, all of which can intensify lung injury and complicate recovery. These same features counsel caution when corticosteroids are used, because connective-tissue fragility raises theoretical concern about wound healing and skin integrity after a major spinal reconstruction, and long-term or high-dose steroid exposure carries recognised skeletal consequences that are particularly unwelcome in a syndrome already associated with bone fragility. A low-dose, time-limited regimen represents a reasonable balance between capturing anti-inflammatory benefit and minimising these hazards.

Aetiology 2: Pulmonary contusion, trauma, and superimposed nosocomial infection

The second patient exemplifies direct pulmonary injury from blunt chest trauma. Pulmonary contusion is a well-established direct risk factor for ARDS, and blunt thoracic trauma carries identifiable prognostic determinants that influence the likelihood of progression to respiratory failure.[14] Mechanistically, any chest trauma, including pulmonary contusion, activates the innate immune system at the site of injury, with local elaboration of cytokines, chemokines, arachidonic-acid metabolites, oxygen radicals, and complement; when this inflammatory response is intense or the volume of injured parenchyma is large, it can precipitate ARDS. The severity and distribution of lung injury therefore shape the clinical phenotype of the pulmonary insult, and the timing of interventions directed at the injured chest wall and lung has measurable consequences for outcome in patients with contusion.[15] Anti-inflammatory adjuncts have accordingly been investigated as a means of attenuating the respiratory complications that follow blunt chest-wall trauma, reflecting the same rationale that underlies corticosteroid use, namely the suppression of an exaggerated inflammatory response to parenchymal injury.[16]

The clinical picture in this patient was complicated by hospital-acquired pneumonia, with sputum cultures growing *Acinetobacter baumannii* and *Enterobacteriaceae*. This superimposed infection matters for two reasons. First, the pathogens responsible for pneumonia can themselves act as inciting or amplifying factors for ARDS, because the immunopathological mechanisms of pneumonia-associated lung injury overlap substantially with those of ARDS, so that infection and contusion may act synergistically to broaden the area of lung involvement. Second, nosocomial pneumonia due to multidrug-resistant organisms, and *Acinetobacter baumannii* in particular, is associated with high mortality and prolonged ventilator dependence in the ICU, and polymicrobial ventilator-associated pneumonia carries a distinct and often worse profile than monomicrobial disease.[17,18] Large multicentre surveillance data confirm that multidrug-resistant infections, prominently including *Acinetobacter* species and resistant *Enterobacterales*, are major drivers of mortality in adult intensive-care units.[19] This infective dimension sharpens the central tension of corticosteroid use, because immunosuppression in the setting of an incompletely controlled resistant infection could in principle be harmful. It was for this reason that corticosteroids were introduced only after

appropriate antimicrobial cover was established and the inflammatory contribution to hypoxaemia was judged to predominate, and it is reassuring that contemporary syntheses have not demonstrated a significant increase in secondary-infection rates at the low doses employed.[5,20] The broader critical-care literature offers a useful parallel here: in community-acquired pneumonia complicated by septic shock, subgroup analysis of a phase 3 randomised trial demonstrated benefit from low-dose corticosteroid therapy, reinforcing the principle that steroids can be advantageous even when infection is the proximate trigger, provided that antimicrobial treatment is concurrent and adequate.[21] This patient's course, in which corticosteroids were layered onto rather than substituted for targeted antimicrobial therapy, is consistent with that principle.

Lung-protective ventilation as the shared therapeutic foundation

It must be emphasised that corticosteroids in both patients were an adjunct to, and never a substitute for, meticulous lung-protective ventilation. The management of ARDS rests principally on low tidal-volume ventilation, conservative fluid management, and individualised PEEP titration aimed at minimising driving pressure, measures that constitute the evidence-based mainstay of care in severe disease. Contemporary randomised and physiological studies continue to refine how PEEP should be individualised, whether by transpulmonary driving-pressure-guided titration in ARDS or by patient-specific approaches that account for body habitus, in order to optimise recruitment while limiting overdistension and ventilator-induced lung injury.[22,23] In the first patient, PEEP was maintained at 10 cmH_2O during the acute phase and weaned to 6 cmH_2O as oxygenation recovered; in the second, higher PEEP levels of 14 cmH_2O were required initially and were subsequently reduced as gas exchange improved and the patient was liberated to a non-rebreathing mask. The parallel improvement in radiographic appearance and PaO_2/FiO_2 in both patients reflects the combined effect of protective ventilation and adjunctive anti-inflammatory therapy, and it would be inappropriate to attribute recovery to corticosteroids in isolation.

The concept of driving pressure, defined as the difference between plateau pressure and PEEP and reflecting the ratio of tidal volume to respiratory-system compliance, has become central to how protective ventilation is individualised. Setting PEEP to minimise driving pressure, rather than pursuing any fixed value, aligns the delivered tidal volume with the size of the aerated lung available to receive it, and thereby limits both cyclic overdistension and repetitive alveolar collapse. Physiological studies employing transpulmonary-pressure-guided titration report that this approach can improve the prognosis of patients with ARDS by tailoring PEEP to the individual respiratory mechanics rather than to a population average.[22] The recognition that body habitus and chest-wall mechanics substantially modify the pressure required to keep the lung open has similarly prompted trials of patient-specific PEEP selection, underscoring the same individualising philosophy that governs corticosteroid decision-making.[23] In the two patients reported here, PEEP was adjusted dynamically as compliance and oxygenation evolved, being weaned from 10 to 6 cmH_2O in the first patient over five days and reduced stepwise from 14 cmH_2O in the second as the contused and infected lung recovered, illustrating in practice the principle that ventilator settings in ARDS are not static prescriptions but continuously titrated responses to a changing lung.

Balancing benefit against harm

The decision to use corticosteroids in any ARDS patient requires an explicit weighing of benefit against harm. Among the adverse effects of glucocorticoids, hyperglycaemia is the most consistently observed, and it was anticipated and monitored in both patients; by contrast, low-dose regimens have not been shown to increase gastrointestinal bleeding or, importantly, secondary infection to a statistically significant degree in pooled analyses.[5] A contemporary review of low-dose corticosteroids in critically ill adults with severe pulmonary infection reinforces the position that, when confined to low doses and appropriate indications, the risk-benefit

balance can favour treatment, while cautioning that patient selection remains paramount.[24] Evidence specific to glucocorticoids in ARDS has similarly indicated that among the available agents, methylprednisolone in particular has been associated with reduced mortality and increased ventilator-free days without a demonstrable excess of ventilator-associated pneumonia or hyperglycaemic events in the analysed cohorts.[20] In patients with connective-tissue fragility, such as the first patient, vigilance must extend to glycaemic control, skin integrity, and musculoskeletal function, given the theoretical interaction between corticosteroid exposure and the tissue vulnerability inherent to Marfan syndrome. The judicious, low-dose, time-limited approach adopted here reflects an attempt to secure the anti-inflammatory benefits suggested by randomised evidence while respecting these patient-specific hazards.

Towards phenotype-guided immunomodulation

The two cases, viewed together, gesture towards a future in which the decision to use corticosteroids in ARDS is guided less by the presence of the syndrome as a whole and more by the biological state of the individual patient. At present, the bedside clinician must infer the inflammatory context from indirect signals, the abruptness of onset, the nature of the precipitating insult, the trajectory of gas exchange, and readily available markers such as the white-cell count, lactate, and the pattern of radiographic change. Both patients in this series displayed features suggestive of a strongly inflammatory process amenable to immunomodulation, and both improved. Yet inference of this kind is imperfect, and the field is moving towards biomarker- and phenotype-enriched approaches in which measurable inflammatory signatures, rather than clinical impression alone, identify the patients most likely to benefit.[3] The demonstration that subphenotypes are temporally stable is particularly encouraging, because it implies that a phenotype ascertained early can guide therapy over the ensuing days rather than shifting unpredictably. Network comparisons of the major adjunctive therapies further suggest that the optimal choice among corticosteroids, neuromuscular blockade, and other interventions may itself be phenotype-dependent, so that the question is not simply whether to treat but which agent suits which patient.[7] Until such tools are validated and widely available, a pragmatic strategy that combines careful clinical phenotyping, early low-dose corticosteroids in inflammatory presentations, and rigorous attention to infection control offers a defensible middle path, and it is this strategy that the present series illustrates.

Strengths, limitations, and implications

The principal strength of this report is the contrast it draws between two aetiologically distinct forms of ARDS managed with a common adjunctive strategy, which illuminates the practical meaning of ARDS heterogeneity at the bedside. Several limitations must be acknowledged. As an uncontrolled two-patient series, it cannot establish causality; the favourable trajectories are consistent with a corticosteroid effect but are equally compatible with the natural resolution of transfusion-related injury and contusion under optimal supportive care. Detailed physiological data such as driving pressure, static compliance, and serial inflammatory biomarkers were not available to characterise the subphenotype directly, so the inference that both patients were inflammatory responders remains clinical rather than biomarker-confirmed. It should also be acknowledged that the initial tidal volume recorded in the first patient, 300 mL, corresponds to approximately 9.7 mL/kg of actual body weight and therefore exceeded the 6 mL/kg of predicted body weight recommended for lung-protective ventilation; this setting reflected the immediate post-operative transfer condition and was adjusted downward as protective ventilation was established, but the deviation is noted here as a limitation and a reminder that tidal volume in ARDS should be indexed to predicted rather than actual body weight. The diagnosis of transfusion-related acute lung injury in the first patient was made on clinical and temporal grounds rather than by specific antibody testing, and alternative or coexisting contributors, including the renal impairment and elevated lactate present at admission, cannot be entirely excluded. In the second patient, the relative contributions of contusion, infection, and

corticosteroid therapy to recovery cannot be disentangled. Finally, the absence of long-term follow-up precludes any conclusion about pulmonary function or fibrosis after discharge. These limitations notwithstanding, the series supports a clear clinical message: rather than applying or withholding corticosteroids uniformly, clinicians should reason from aetiology and inflammatory context, favour early low-dose regimens, secure infection control before immunomodulation where infection is present, and regard corticosteroids as an adjunct to, not a replacement for, lung-protective ventilation. Prospective, phenotype-enriched trials remain necessary to define which ARDS patients derive the greatest net benefit from corticosteroid therapy.

4. Conclusion

ARDS arising from diverse aetiologies remains a formidable threat to patients and a persistent challenge to clinicians. These two patients, one with post-transfusion acute lung injury on a background of Marfan syndrome and one with trauma-related ARDS from pulmonary contusion complicated by multidrug-resistant nosocomial pneumonia, developed severe hypoxaemia through fundamentally different mechanisms yet followed strikingly similar paths to recovery when treated with early, low-dose intravenous methylprednisolone layered upon lung-protective ventilation and, where relevant, targeted antimicrobial therapy. Their courses illustrate that the value of corticosteroids in ARDS is neither universal nor negligible but conditional, and that this condition is best defined by aetiology, inflammatory phenotype, dose, and timing. In the patient with Marfan syndrome, connective-tissue fragility and cardiovascular vulnerability complicate management and demand additional caution during steroid exposure, while in the patient with pulmonary contusion, superimposed resistant infection widens the area of lung injury and requires that immunomodulation follow, rather than precede, effective source control. Early recognition, individualised lung-protective ventilation, careful patient selection, and closely monitored low-dose corticosteroid therapy together offer a rational framework for improving recovery in selected patients with ARDS, and they reinforce the broader principle that heterogeneous syndromes are best served by individualised rather than uniform care.

Declarations

Ethics approval and consent to participate

This case series was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for the use of clinical data and de-identified radiographic images for educational and publication purposes was obtained from the patients or their legal guardians. All images were reviewed to ensure that no patient-identifying information was included.

Consent for publication

Written informed consent for publication of clinical details and accompanying images was obtained from the patients or their families. The radiographs reproduced here contain only anatomical and laterality markers and carry no personal identifiers.

Availability of data and materials

The clinical data supporting the findings of this report are available from the corresponding author on reasonable request, subject to institutional confidentiality requirements.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the clinical management of the patients, the acquisition and interpretation of data, the drafting and critical revision of the manuscript, and approved the final version for submission.

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