



# Should high-dose steroid therapy and inhaled nitric oxide be considered for adult patients with H1N1 respiratory failure?

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## DECLARATIONS

Steroids and inhaled nitric oxide (iNO) are not recommended in acute respiratory distress syndrome (ARDS) secondary to H1N1 pneumonia; nevertheless, their effects could benefit in specific cases.

## Competing interest

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## Ethical approval

Ethical approval was not sought as the report is a retrospective review of a clinical case, but the written consent of the patient has been obtained.

## Guarantor

FC

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## Clinical case

In late 2010 a 38-year-old sportswoman, non-smoker, with no history of respiratory or other diseases was admitted to the intensive care unit (ICU) with respiratory failure secondary to H1N1 influenza A pneumonia. The H1N1 influenza A virus was confirmed by realtime reverse transcription polymerase chain reaction from a nasopharyngeal swab. The patient had a history of eight days of cough and increasing pyrexia. On presentation in Accident and Emergency Department she was tachypnoeic (42 breaths per minute) and hypoxic (oxygen saturation on room air 68% with PaO<sub>2</sub> [partial pressure of oxygen in arterial blood] 5 kPa). Her heart rate was 115 beats per minute and arterial blood pressure 85/45 mmHg. Chest radiograph showed bilateral widespread opacifications. She was intubated and transferred to the ICU. Initial organ support consisted of ventilation on 100% oxygen and noradrenaline infusion. Oseltamivir, intravenous Augmentin and Clarithromycin were started. After six hours of pressure control ventilation on 100% oxygen aiming at tidal volumes of 6 mL/kg of predicted body weight, refractory hypoxia necessitated ventilatory support with high frequency oscillatory ventilation (HFOV). The patient developed multiorgan dysfunction syndrome (MODS) including acute kidney injury requiring renal replacement therapy. Taking into account insensible losses, daily fluid balance was

neutral or negative in accordance with ARDSnet guidelines.<sup>1</sup> Eleven days after admission she remained on HFOV and oxygen requirements continued to be high achieving PaO<sub>2</sub> of 9 kPa on F<sub>I</sub>O<sub>2</sub> (fraction of inspired oxygen) of 0.95. Although she was a suitable candidate for extracorporeal membrane oxygenation (ECMO), this resource was not available due to the large number of patients with H1N1 influenza A virus requiring ECMO at that time. The patient was medically unfit to transfer for computed tomography of the thorax, but sequential chest radiographs showed progressive lower zone consolidations and bilateral pleural effusions. There was a concern that obliterative bronchiolitis was developing as H1N1 influenza A virus which has potential for causing small airways disease. This was the rationale for prescribing methylprednisolone which was given in a dose of 1 g daily for three days (days 11, 12, 13 since ICU admission). Contraindications to steroids were not present as although the C reactive protein was 149 mg/L, there were no signs of acute intercurrent infection. After three days of steroid treatment (day 14 since ICU admission) noradrenaline was stopped and C reactive protein fell to 6.2 mg/L. Although administration of steroids was followed by an improvement in haemodynamic status and a fall in inflammatory markers, gas exchange remained poor. Therefore, iNO in the dose of 21 ppm (parts per million) was started (day 14 since ICU admission) in an attempt to improve pulmonary blood flow and possibly gas exchange. Within one hour of commencing of iNO there was an increase in PaO<sub>2</sub> from 8.63 to 14.5 kPa while on F<sub>I</sub>O<sub>2</sub> 0.9, and to 18.8 kPa four hours later. The F<sub>I</sub>O<sub>2</sub> requirements continued to decrease and she was on F<sub>I</sub>O<sub>2</sub> 0.55 on the following day (day 15 since ICU

admission). iNO was given for three days and stopped as oxygenation improved (PaO<sub>2</sub> of 10.8 kPa on F<sub>I</sub>O<sub>2</sub> 0.45). On day 16 (third day with iNO) HFOV was stopped and protective pressure controlled ventilation commenced. The patient started to produce urine and when electrolytes and creatinine normalized, renal replacement therapy was stopped. A percutaneous tracheostomy was performed to facilitate weaning from respiratory support and on the 19th day she was commenced on pressure support ventilation. At this time a computed tomography scan demonstrated diffuse symmetrical multifocal peribronchovascular ground glass consolidative opacity most prevalent in the lung bases with evolving bronchiectasis. The patient made good recovery and was transferred to the ward following 33 days in the ICU.

## Discussion

Our 38-year-old patient previously very fit and healthy developed a life-threatening ARDS secondary to H1N1 influenza A virus pneumonia. She was not responding to management in line with ARDS network recommendations<sup>1,2</sup> including antiviral and antimicrobial therapy, and full ICU support with noradrenaline, HFOV and renal replacement. We were of the opinion that the severity of her condition rendered survival unlikely, particularly given lack of availability of ECMO at the time.

The 2009 World Health Organization guidance on pandemic influenza does not recommend the routine use of corticosteroids for treatment of H1N1 influenza A infection.<sup>3</sup> Steroid therapy is controversial in the subacute ARDS setting, and has been shown to be harmful when initiated more than two weeks after the onset of the syndrome.<sup>4</sup> Possible risks associated with steroids use include secondary infections, hyperglycaemia, poor wound healing, prolonged muscle weakness with impaired functional status, psychosis and pancreatitis. Nevertheless, we opted for a high dose of methylprednisolone, as a rescue therapy, on the 11th day of this patient's critical illness while carefully balancing potential risks and benefits. There was some evidence of developing obliterative bronchiolitis in the absence of an ongoing infection. The dose and duration of therapy were in line with what is

advised for the management of obliterative bronchiolitis following lung transplant.<sup>5</sup> The rationale behind our decision was that the lung damage was thought to be largely related to an immunologically mediated process at that stage of this patient's illness. In our patient, administration of methylprednisolone was followed by a decrease in markers of systemic inflammatory response and an improvement in the haemodynamic status. Furthermore, there was also an improvement in patient's oxygenation subsequent to iNO administration. Although it coincided with iNO administration, this improvement could also have been contributed by the pathophysiological effects of steroids which include a reduction in airway and parenchymal inflammation and the potential for preventing obliterative bronchiolitis and pulmonary fibrosis.<sup>6-8</sup> In fact, the improvement in oxygenation has been sustained after stopping iNO which would point towards beneficial effect of steroids.

The use of iNO in hypoxic respiratory failure due to ARDS in adults is debatable. iNO diffuses across the alveolar-capillary membrane into the smooth muscle of pulmonary vessels and activates soluble guanylate cyclase. This enzyme starts the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). Increased intracellular concentration of cGMP relaxes smooth muscle. In contrast to intravenously administered vasodilators, iNO is a selective agent for two important reasons: it is scavenged by haemoglobin and is thereby rapidly inactivated, limiting its vasodilatory effect to the lung while avoiding systemic effect; moreover, it increases blood flow only in well-ventilated lung areas reducing intrapulmonary shunting. Potential toxic effect of iNO can be accounted for by multiple effects: increases in cGMP can alter normal cellular proliferation; iNO can cause potentially mutagenic DNA alterations; it can rapidly react with oxygen to form nitrogen dioxide (lung irritant) and with superoxide anion to form a cytotoxic oxidant that can interfere with the surfactant function. Out of lungs effects include interference with platelet aggregation and methemoglobinaemia.<sup>9</sup> But there is little evidence of such toxicity when iNO is kept in a concentration below 80 ppm. The latest Cochrane review on the use of iNO in ARDS in adults found a significant improvement in oxygenation in the first 24 hours although it

did not show any statistically significant effect on overall mortality, duration of ventilation, ventilator-free days and on the duration of stay in the ICU and hospital.<sup>10</sup> Despite uncertainty of beneficial effect of iNO highlighted by the literature, in the present case we administered iNO as a rescue therapy after a three-day course of steroids in an attempt to improve oxygenation. The instant improvement in oxygenation we observed may be attributed to iNO-mediated pulmonary vasodilation, but the sustained effect may indicate a potential synergism with the anti-inflammatory and antiproliferative effects of methylprednisolone.

Although one can draw limited conclusions from a case report, the temporal association between the administration of methylprednisolone and iNO with significant clinical recovery suggests a potentially beneficial role of these agents in H1N1 influenza A-related ARDS in adults.

## Conclusion

Methylprednisolone supplemented with iNO may play a role in selected patients with H1N1 influenza A related pneumonia and refractory respiratory failure for whom no other treatments (particularly ECMO) are available. Further studies are necessary to confirm this observation.

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