Cardiology in the Young

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Recombinant angiotensin II therapy in a child with cardiac dysfunction and *Pandoraea* and *Candida* sepsis

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Brief Report

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Abstract

Recombinant angiotensin II is an emerging drug therapy for refractory hypotension. Its use is relevant to patients with disruption of the renin–angiotensin–aldosterone system denoted by elevated direct renin levels. We present a child that responded to recombinant angiotensin II in the setting of right ventricular hypertension and multi-organism septic shock.

The renin–angiotensin–aldosterone system is a hormonal axis responsible for blood pressure regulation and fluid balance.[1] Disruption of this system leads to hypotension, fluid shifts, and electrolyte derangements.[2] Several mechanisms responsible include pro-inflammatory conditions, endothelial injury, and end-organ damage.[2] Classically, critically ill patients with vasoplegia and hypotension are managed with vasoactive agents including vasopressin, epinephrine, norepinephrine, and dopamine.[3]

While vasopressors are effective and recommended for the management of sepsis and circulatory shock, there are instances in which patients become tolerant or respond sub-optimally to therapy.[1] Recombinant angiotensin II has been studied as a potential adjunctive therapy in patients identified as "responders" denoted by elevated renin levels [1, 4]. This patient subtype has been described in both the adult and paediatric population by achieving a normotensive state and discontinuing from other vasoactive therapies.[1,4–7] The medication's utility in patients with cardiac dysfunction has not been fully described. There are promising results with its use in adult and paediatric cardiac surgery patients liberating from cardiopulmonary bypass.[8]

We present a paediatric patient with cardiac dysfunction and septic shock who received recombinant angiotensin II therapy.

Case presentation

The patient is a previously healthy 19-month-old female with a history of intermittent febrile illnesses 3 months prior to initial presentation. She was diagnosed with bilateral necrotising pneumonia ultimately requiring veno-venous extracorporeal membrane oxygenation due to acute respiratory distress syndrome. She remained on ECMO throughout her clinical course. She was referred to our institution for lung transplant evaluation. Respiratory cultures from the prior institution grew *Acinetobacter spp* and gram-negative rods. She was positive for adenovirus and her urine cultures grew *Candida spp*.

Upon transfer she was haemodynamically stable with significant sedation. The therapeutic goals were to rehabilitate her lungs and treat residual infection to formally evaluate for lung transplantation. Initial echocardiogram demonstrated normal cardiac anatomy with no right ventricular hypertension. She initially improved with serial bronchoscopies and ventilator manipulation. Her bronchoalveolar lavage cultures grew *Candida parapsilosis*. She had respiratory cultures that grew gram negative rods that did not speciate (day 1) and methicillin-susceptible *Staphylococcus aureus* (day 8). On day 9, she developed fluid overload and metabolic acidosis requiring initiation of continuous renal replacement therapy. She grew *Staphylococcus aureus* from her blood culture on day 11.

On day 16, she developed hemodynamic instability and became more hypotensive over the next 48 hours with extremely labile blood pressures despite epinephrine, norepinephrine, and vasopressin infusions, inhaled nitric oxide, steroids, and aggressive fluid replacement. Her blood cultures grew *Candida parapsilosis* which prompted treatment with antifungal therapy and removal of her indwelling central line. Echocardiogram revealed right ventricular hypertension, mild right ventricular dilation with diminished function, mild to moderate tricuspid valve regurgitation, and normal left ventricular systolic function. She received pulmonary vasodilator therapy including inhaled nitric oxide at 20 ppm (maximum dose 40ppm).

On day 17, due refractory hypotension on multiple agents (epinephrine 0.2 mcg/kg/min, norepinephrine 0.16 mcg/kg/min, vasopressin 2 milliunits/kg/min), we used recombinant angiotensin II (Giapreza™, La Jolla Pharmaceuticals, San Diego) with an initial starting dose of 10 ng/kg/min. Her baseline renin level was 4284 pg/mL (ref 3.2 – 52.2 pg/ml), indicating a high likelihood for response. Subsequent renin levels were 5776 (24 hours from initial level) and > 6000 (48 hours from initial level). Within 1 hour of initiation, her blood pressure normalised and her other infusions were tapered successfully. She clinically progressed over the next 24 hours until she became labile again despite titrating as high as 40 ng/kg/min. Her condition deteriorated and she required CPR on day 20. Her family decided to withdraw care due to her ongoing hemodynamic instability, end organ dysfunction, and persistent fungemia on day 22.

Autopsy demonstrated diffuse, necrotising pneumonia with near-complete liquefaction of the left upper lobe and innumerable seeded foci. Bacterial, fungal, and mycobacterial cultures of lung tissue were collected. Mycobacterial cultures showed "no growth" and direct tissue fungal cultures grew *Candida parapsilosis*. Bacterial cultures grew a gram-negative bacilli that was not identifiable using the bioMerieux Vitek MS MALDI-ToF (Mass Spectrometry Time of Flight) system. DNA was extracted from colonies and sent to our DNA Sequencing and Genotyping Core Laboratory. Top results from BLAST nucleotide search of the sequence of the 16 sRNA region were *Pandoraea pulmonicola* (99.63%), *Pandoraea nosoerga* (97.35%), and *Pandoraea thiooxydans* (97.21%). The *Pandoraea spp.* is suspected to be the same organism that was growing from her initial respiratory cultures at the outside institution.

Discussion

Pandoraea spp. are antibiotic resistant, pathogenic Gram negative rods that reside in the soil and the environment.[9] Infections have mostly been reported in patients with cystic fibrosis.[9] In our review of the literature, this is the first documented paediatric patient without cystic fibrosis to have bacteraemia with this species. One possible contributing factor in this patient is an immunodeficiency given she had an abnormal neutrophil burst assay and treatment-resistant polymicrobial infections. Postmortem testing revealed a variant of unknown significance in a relevant gene implicated in chronic granulomatous disease.

Recombinant angiotensin II is a novel vasoactive therapy in those identified as responders. Studies have shown correlation with elevated renin levels and an anticipated response of blood pressure.[1,4,6,7] It has also been described that patients with elevated renin levels receiving standard vasoactive therapy have poorer outcomes.[2]

Management of distributive shock and cardiac dysfunction is challenging. There is competition with optimising preload, contractility, and afterload reduction while maintaining adequate end-organ perfusion in a vasoplegic state. In an acidotic state, cardiac function is compromised which also decreases efficacy of inotropes.[3] Post-cardiopulmonary bypass is another scenario where patients respond unpredictably to vasoactive therapies and suffer from low cardiac output.[10]

Recombinant angiotensin II is a unique therapy that facilitates rapid vasoconstriction utilising the body's natural hormonal axis. Identifying "responders" to therapy would provide new management strategies in the setting of sepsis or inflammation. Given that it was used as a last resort in our patient, understanding optimal timing, dosing, and patient "responders" is critical for its future utility.

Conclusion

Management of septic shock with cardiac dysfunction has no ideal therapeutic options. Traditional pharmacologic and supportive options are still the standard of care. Recombinant angiotensin II is a potential pharmacologic intervention that may be an alternative therapy for this scenario.

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Conflicts of interest. None.

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