Colchicine: An Impressive Effect on Posttransplant Capillary Leak Syndrome and Renal Failure

Enrico Cocchi, MD,‡ Federica Chiale, MD,‡ Bruno Gianoglio, MD,† Luca Deorsola, MD,§ Carlo Pace Napoleone, MD,‡ Franca Fagioli, MD,§ Licia Peruzzi, MD‡

Capillary leak syndrome is a critical condition occasionally occurring posttransplant and is characterized by acute endothelial hyperpermeability leading to systemic protein-rich fluid extravasation and consequent hypovolemia, hypoperfusion, and acute kidney injury. Treatment is merely supportive and is based on osmotic drugs, diuretics, continuous renal replacement therapy, and surgical drainage. However, removal of the underlying inflammatory cause is mandatory to achieve stable resolution. Herein, we report the first successful treatment with colchicine in 2 life-threatening pediatric cases of capillary leak syndrome with renal failure occurring after transplant (heart and bone marrow) and unresponsive to any other line of therapy. Both cases were only palliated by supportive therapy and revealed an impressively rapid response to colchicine both in terms of diuresis and clinical condition recovery, allowing for the cessation of renal replacement therapy in a few hours. In both patients, colchicine was temporarily discontinued for transient leukopenia (attributed to an additive effect with mycophenolate mofetil), resulting in extravasation, and renal failure recurrence was restored only after colchicine reintroduction. Although the association of colchicine with an immunosuppressive drug was formerly contraindicated, no other adverse events were noted when using a minimized dose. Both patients are now maintaining a good renal function without recurrence of extravasation after 6 months of follow-up. In conclusion, this strikingly positive experience forces physicians to consider this old and cost-effective drug as a new, powerful rescue tool in such critical cases.

abstract

Dr Cocchi conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Chiale, Deorsola, Pace Napoleone, Gianoglio, and Fagioli designed the data collection instruments, collected data, and reviewed and revised the manuscript; Dr Peruzzi was actively involved in both cases’ management, conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2018-2820

Accepted for publication Dec 18, 2018

Address correspondence to Enrico Cocchi, MD, University of Turin, Nephrology, Dialysis and Transplantation Unit, Pediatric Cardiac Surgery Unit, and Pediatric Oncology-Hematology Unit, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children’s Hospital, Turin, Italy

Copyright © 2019 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

CLS occasionally occurs in a posttransplant setting in which fluid overload and impaired fluid balance are strongly related with mortality. In fact, massive fluid extravasation leads to peripheral hypoperfusion and renal impairment, often resulting in prerenal acute kidney injury (AKI). In early phases, treatment is merely supportive and based on reattracting fluids from third space to effective circulating volume (ECV) by using osmotic agents, such as albumin, followed by net fluid elimination with diuretics. Nevertheless, when fluid accumulates in body cavities and interferes with vital organ function, a surgical drainage is mandatory. This approach is normally sufficient to support the patient until resolution of the extravasation-underlying cause. Nevertheless, in some critical cases, extravasation severity and speed exceed treatment efficiency, and AKI progresses, requiring continuous renal replacement therapy (CRRT) to ensure proper fluid balance. In case of persistence of the inflammatory noxa, spontaneous resolution is rarely achievable, and clinical management of the patients represents a difficult challenge, especially in children. In such cases, rescue treatments beyond traditional care become necessary.

Herein, we present our positive experience with colchicine in 2 children who developed a severe CLS rapidly evolving to anuric AKI after heart and bone marrow transplant that was unresponsive to any other line of treatment.

CASE PATIENTS

Patient 1
A 17-year-old boy was born with an univentricular heart treated by using pulmonary artery banding, bidirectional Glenn, and extracardiac Fontan interventions in infancy, complicated by severe plastic bronchitis and Fontan-associated liver disease with advanced hepatic fibrosis (FibroScan 12 kPa, corresponding to Metavir grade F4). He received an orthotopic heart transplant with standard thymoglobulin-steroid induction, tacrolimus, mycophenolate mofetil (MMF), and steroid maintenance.

Since day 1 posttransplant, he experienced severe fluid leakage up to 3000 to 4000 mL/day, initially limited to mediastinum and identified as lymph. After a few days of partial resolution, leakage became multisystemic (pleural, peritoneal, and subcutaneous) with a composition similar to plasma.

He developed oligoanuric AKI, requiring CRRT from the second posttransplant day.

Because of persistent extravasation, on day 59, thoracic duct ligation was performed, which was partially successful in reducing the mediastinal effusions (Fig 1). Nevertheless, oliguria progressed to anuria and increased fluid overload (Fig 1) despite normal right and left ventricular function and renal perfusion. Additional corticosteroid pulses and anti-inflammatory drugs were unsuccessful. Progressive decline of general conditions led to a rescue attempt with colchicine on day 97.

Patient 2
A 12-year-old girl affected by trisomy 21 and Tetralogy of Fallot corrected at 3 months developed an M6 acute myeloid leukemia at age 4 and acute lymphoblastic leukemia at age 11. She was effectively treated with chemotherapy and hematopoietic stem cell transplant (HSCT) 7 months later.

On day 23 posttransplant, she developed oliguric AKI, which gradually resolved after nephrotoxic drug withdrawal (acyclovir, vancomycin, and amikacin), allowing for her to be discharged on day 31 with mild renal impairment (estimated glomerular filtration rate [eGFR] 48.9 mL/minute per 1.73 m²) and under maintenance therapy with cyclosporin and prednisone.

Since HSCT, she presented with 3 AKI episodes characterized by increased serum creatinine and C-reactive protein (CRP), bilateral pleural effusions requiring thoracentesis and vacuum up to 20 days, ascites, and diffuse peripheral edema. The presentation was always dominated by respiratory distress and fever, rapidly evolving to multiple effusions and AKI. The first 2 episodes (days 44 and 179) occurred during prednisone tapering and were effectively controlled by intravenous methylprednisolone pulses (2–5 mg/kg per dose). The third episode (day 347) initially responded to methylprednisolone pulses (10 mg/kg every other day) and MMF (600 mg/m²), but subsequent effusions and oliguria worsened until CRRT requirement.

The severity of systemic effusion, despite increased immune suppression, led to a rescue attempt with colchicine.

RESULTS

Colchicine Mechanism of Action on Vascular Endothelial and Extravasation

Colchicine’s precise impact on vasculature is still unknown, and specific literature on the topic is lacking.

In fact, although colchicine’s best-known effect is arresting microtubule polymerization at high dosage, it also exerts several anti-inflammatory effects on both macrophages and endothelial cells through modulation of VCAM-1, tumor necrosis factor α, E-selectin, interleukin 1b, and NLRP3 inflammasome. However, no clear explanation of its effect on extravasation is provided in the literature. This effect may also be attributable to its in vivo antiapoptotic action, considering that
endothelial cell apoptosis appears to play a role in CLS pathogenesis.\textsuperscript{18,19} Altogether, this multisite action may reduce both endothelial permeability and extravasation of high–molecular weight molecules, such as albumin, but additional studies are needed to clarify the exact effect of colchicine on vasculature.

**Effects of Colchicine on Hypoalbuminemia and Blood Pressure**

Both patients presented with massive hypoalbuminemia without albuminuria in addition to hypotension, hemoconcentration, and generalized edema. Hypoalbuminemia persisted until extravasation resolution despite massive albumin supplementation (1–2 g/kg per day) and highly caloric total parenteral nutrition. At the same time, in both patients, hypotension persisted despite fluid administration in accordance with the guidelines of shock management, requiring continuous endovenous sympathomimetic amine support in patient 1.

Both albuminemia and blood pressure normalized in a few days after colchicine administration, presumably through fluid compartment reequilibration (Fig 2).

**Cardiac Function**

Both patients had normal cardiac function; patient 1 was affected by severe mediastinal effusion requiring drainage, whereas patient 2 had only mild pericardial effusion. In both cases, cardiac function was monitored daily by using echocardiography during the acute extravasation phase, revealing normal ventricular function and excluding a cardiac etiology for such fluid overload.

**Effects of Colchicine on Diuresis and Fluid Balance**

The initial dose of colchicine was $10\,\mu\text{g/kg per day}$ ($0.5\,\text{mg/day}$).
modulated in consideration of renal failure.

ECV hypovolemia was extremely pronounced in both patients and only partially responsive to fluid administration. After colchicine administration, diuresis was restarted in a few hours, and 48 hours later, a net-negative fluid balance was achieved (Fig 1), allowing for CRRT discontinuation. The end of the “inflammatory crisis” was defined by massive polyuria in both patients, as is characteristic of CLS resolution.\(^1\)

It is worth noting that CRRT could be stopped after more than 3 months (day 108) in patient 1, when renal failure was considered irreversible by this time.

Extravasation Recurrence at Suspension

In both cases, systemic extravasation with hypoalbuminemia, oliguria, and fluid overload recurred shortly after colchicine discontinuation due to transient leukopenia (interpreted as additive effect with MMF), further revealing its antievacuation effect. In patient 1, recurrence was almost immediate, with pericardial and pleural effusions requiring drainage within 5 days from colchicine discontinuation.

Patient 2 experienced bilateral pleural effusions, ascites, and AKI, requiring CRRT after a latency of 14 days.

Colchicine Reintroduction

In both cases, colchicine was reintroduced after leukopenia recovery. In patient 1, this took place 8 days after withdrawal with a strikingly rapid response similar to that observed after primary colchicine introduction.

In patient 2, colchicine was reintroduced after 39 days, initially obtaining only a partial response and evolving into complete resolution after dose doubling (1 mg daily).

Inflammatory Markers

Both patients had normalized serum CRP only after colchicine introduction (Fig 1), suggesting its capacity to interrupt the inflammatory mechanism behind the capillary leak, which was always associated with serum CRP increments but never associated with any evidence of infections.

Patient Discharge and Follow-up

Patients were discharged with colchicine maintenance at a minimized dose of 2.5 µ/kg per day (0.125 mg/day) under strict follow-up.

Patient 1 was discharged on day 143 after transplant with colchicine and tacrolimus without MMF nor steroids. Until now (day 320), no recurrence of extravasation and stable renal function (eGFR 60 mL/minute per 1.73 m\(^2\)) were achieved.

Patient 2 was discharged on day 467 after HSCT and experienced a transient central venous catheter–related sepsis on day 487. It is noteworthy that during this episode, an initially mild bilateral pleural effusion without significant diuresis impairment was controlled by using colchicine dose doubling without a need for additional steroids.

There are no clear indications for colchicine therapy duration. On the basis of actual experience from inflammatory diseases, it can range from 1 to 18 months, depending on patient response and adverse effects.\(^9,20\) We will evaluate colchicine dose requirements through follow-up in both cases, and tapering will be attempted after 12 months, according to patient status.
Safety, Interaction, and Adverse Events

Parents gave informed consent to the colchicine treatment as a third-line rescue therapy to be considered as an extension of the approved pericardial effusion indication.

In case 1, a colchicine-tacrolimus interaction developed without impact on daily monitored tacrolimus levels. Colchicine was modulated in both cases according to the leucocyte count because of drug level unavailability. Mild leucopenia was initially observed in both cases, attributed to additive MMF effect, and resolved with colchicine and MMF discontinuation. No infections occurred in patient 1. Patient 2 has transient central venous catheter–related sepsis, which was unrelated to leucopenia.

No other adverse effect was recorded.

DISCUSSION

Severe CLS leading to a hemodynamically relevant third space with anuria requiring CRRT may represent a serious life-threatening event, especially within the complex transplant setting.

In our cases, CLS occurred under full immune suppression and was unresponsive to any line of treatment, whereas colchicine proved a successful option.

Although primary pathogenic subsets might be conceivably different, both cases shared a similar course: massive CLS with a rapid progression to anuric AKI requiring CRRT. Fluid extravasation was interrupted only by colchicine, resulting in renal perfusion and diuresis normalization. The colchicine effect was additionally revealed by the extravasation relapse a few days after treatment was stopped and subsequent reversal after its reintroduction.

It is worth noting that, although formerly contraindicated, the drug was safely administered during immunosuppressive therapy and AKI at a reduced dose.

To the best of our knowledge, this is the first report of a severe third-space AKI attributable to CLS in a transplant setting effectively controlled with colchicine.

This empirical observation in 2 different transplant settings and the absence of significant side effects led physicians to consider colchicine as a useful option in posttransplant CLS and renal failure in which CRRT weaning is mandatory to ensure transplant success and patient survival without additional morbidity.

Additional exploration of the potential use of colchicine in posttransplant systemic fluid effusion is advocated.

ACKNOWLEDGMENTS

We acknowledge the physicians and nurses of the cardiac intensive care, dialysis, onco-hematology, nutrition, cardiology, psychology, and rehabilitation units for the great collaborative work and continuous support to the patients and their families, who always encouraged us to try 1 additional rescue effort and gave their consent for publication of these data. We thank Gabriel Oniscu (Scottish Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK) for revising the article.

ABBREVIATIONS

AKI: acute kidney injury
CLS: capillary leak syndrome
CRP: C-reactive protein
CRRT: continuous renal replacement therapy
ECV: effective circulating volume
eGFR: estimated glomerular filtration rate
HSCT: hematopoietic stem cell transplant
MMF: mycophenolate mofetil

REFERENCES

11. Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA. Both positive and negative fluid balance may be associated with reduced long-term...
survival in the critically ill. Crit Care Med. 2017;45(8):e749–e757


Colchicine: An Impressive Effect on Posttransplant Capillary Leak Syndrome and Renal Failure
Enrico Cocchi, Federica Chiale, Bruno Gianoglio, Luca Deorsola, Carlo Pace, Napoleone, Franca Fagioli and Licia Peruzzi
*Pediatrics* 2019;143;
DOI: 10.1542/peds.2018-2820 originally published online April 18, 2019;

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/143/5/e20182820">http://pediatrics.aappublications.org/content/143/5/e20182820</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 22 articles, 4 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/143/5/e20182820#BIBL">http://pediatrics.aappublications.org/content/143/5/e20182820#BIBL</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):  Nephrology <a href="http://www.aappublications.org/cgi/collection/nephrology_sub">http://www.aappublications.org/cgi/collection/nephrology_sub</a>, Surgery <a href="http://www.aappublications.org/cgi/collection/surgery_sub">http://www.aappublications.org/cgi/collection/surgery_sub</a>, Transplantation <a href="http://www.aappublications.org/cgi/collection/transplantation_sub">http://www.aappublications.org/cgi/collection/transplantation_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.aappublications.org/site/misc/Permissions.xhtml">http://www.aappublications.org/site/misc/Permissions.xhtml</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://www.aappublications.org/site/misc/reprints.xhtml">http://www.aappublications.org/site/misc/reprints.xhtml</a></td>
</tr>
</tbody>
</table>
Colchicine: An Impressive Effect on Posttransplant Capillary Leak Syndrome and Renal Failure

Enrico Cocchi, Federica Chiale, Bruno Gianoglio, Luca Deorsola, Carlo Pace Napoleone, Franca Fagioli and Licia Peruzzi

*Pediatrics* 2019;143;
DOI: 10.1542/peds.2018-2820 originally published online April 18, 2019;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/143/5/e20182820