JPPT | Case Report

# *Aspergillus*-Infected Duodenal Perforations Following a Single Dose of Tocilizumab for Pediatric Neuromyelitis Optica

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Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune central nervous system disease with inflammatory events recurring in the optic nerves and spinal cord. Neuromyelitis optica (NMO) is rare in children, and pediatric patients typically present with optic neuritis following infections. Lack of response to pulse-dose intravenous corticosteroids or recurrent relapse episodes warrant therapies such as plasma exchange, intravenous immunoglobulin (IVIG), and rituximab. In adult studies, tocilizumab has been used and found to reduce NMO relapse; however, limitations exist in the pediatric population due to the lack of studies and formal treatment guidelines. Gastrointestinal perforation (GIP) is a rare, life-threatening complication identified in clinical trials during tocilizumab therapy. We report a case of a fatal, infected GIP following a single dose of tocilizumab for refractory NMO in a 15-year-old male. This case highlights the need for more outcomes data when using tocilizumab to treat pediatric NMO. Additionally, an assessment of patient-specific risk factors should be outlined to better direct safe therapy and to minimize negative adverse outcomes.

**ABBREVIATIONS** AQP4, aquaporin-4; CRRT, continuous renal replacement therapy; GIP, gastrointestinal perforation; HD MPD, high-dose methylprednisolone; IV, intravenous; IVIG, intravenous immunoglobulin; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; PLEX, plasmapheresis; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TPN, total parenteral nutrition

**KEYWORDS** case report; invasive fungal infection; neuromyelitis optica; pediatric; tocilizumab

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## Introduction

Optic neuritis is a manifestation that is rarely seen in children compared with adults and is characterized by acute or subacute vision loss. The visual acuity of most children with this condition is close to 20/200 at diagnosis, and the pediatric population is more likely to present with bilateral vision loss.[1] Optic neuritis is commonly seen in children post infection and can be traced to an idiopathic, isolated event. Pulse-dose intravenous (IV) corticosteroids and high-dose oral prednisone tapers are typically the recommended first-line therapy for this condition. However, recurrent relapse episodes warrant the use of therapies such as plasma exchange, IV immunoglobulins, and rituximab. An infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) has been linked to multiple post-infectious manifestations including activation, and triggering of autoimmune diseases. The excess of proinflammatory cytokines during the SARS-CoV-2 infection leaves the immune system in a hyperactive state and may result in the inappropriate creation of auto-antibodies.[2] While there is no known cause of neuromyelitis optica spectrum disorder (NMOSD), several cases of adult patients developing NMOSD after SARS-CoV-2 have been reported.[3]

Tocilizumab, an interleukin-6 inhibitor, is approved for several indications including rheumatoid arthritis and cytokine release syndrome. In adult studies, tocilizumab reduced neuromyelitis optica (NMO) relapse; however, limitations exist in the pediatric population due to the lack of studies and formal treatment guidelines.[4] Authorization of tocilizumab for selected patients with severe SARS-CoV-2 infections has led to increased medication use for other indications.[5] It is important to note, however, that tocilizumab carries a box warning for increased risk of serious infections that could lead to hospitalization or death, specifically in patients on simultaneous immunosuppressants such as corticosteroids. Clinical trials report the second most common adverse effect of tocilizumab to be gastrointestinal perforations (GIPs).[6]

A review of available literature was performed, and similar cases in adult patients have been reported. However, no previously reported cases of GIPs due to tocilizumab occurred after a single infusion. This case is the first, to the authors' knowledge, that highlights the

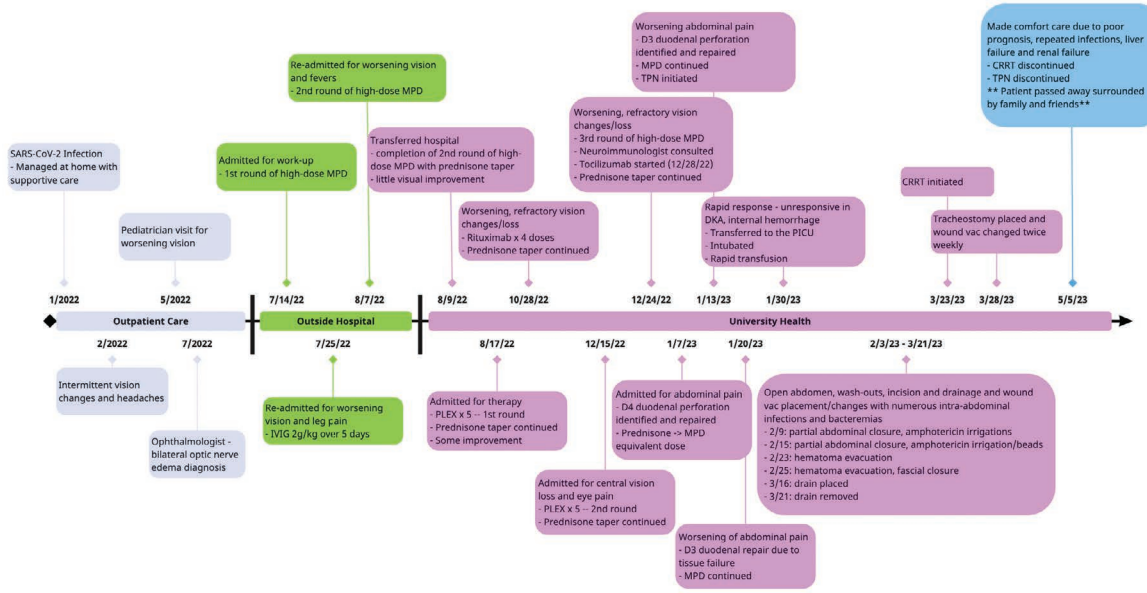
fatal nature of invasive infections from tocilizumab in a pediatric patient with NMO on prolonged, high-dose corticosteroids.

## Case Report

A 15-year-old male weighing 71.7 kg, with a past medical history of resolved SARS-CoV-2 (managed by supportive measures at home), presented with a history of progressive vision loss since February 2022 (see Figure). He was transferred to our facility from an outside hospital for further workup and management following poor response to initial therapies. Initially, he was seen at his pediatrician's office in May 2022, where imaging was performed, notable for Chiari malformation type I, a linear right frontal periventricular hyperintensity, and a subtle hyperintensity within the intra-orbital segment of the right optic nerve. The findings raised concern for demyelinating disease and optic neuritis related to multiple sclerosis. In July 2022, the patient was seen by an ophthalmologist and an eye examination identified bilateral optic nerve edema and hereditary retinal dystrophy bilaterally. He was subsequently admitted to an outside hospital for 500-mg twice daily IV high-dose methylprednisolone (HD MPD) for 3 days, which rapidly resulted in symptom resolution; studies including a lumbar puncture with serologic testing were performed, which ruled out multiple sclerosis as the cause for his vision change. He, however, had a decline in vision, requiring 2 additional admissions at the outside hospital where he received IV immunoglobulin (IVIG) (2 g/kg/day) for 5 days and started HD MPD round 2 before transferring to University Health in August 2022. The second 3-day round of HD MPD was completed and a slow oral prednisone taper beginning at 60 mg daily and decreasing by 5 mg weekly was initiated. He was discharged and readmitted a few days later to receive round 1 of plasmapheresis (PLEX) every other day for 5 sessions with continued prednisone taper. A slight improvement in vision was noted shortly after the PLEX treatment. However, over the next 2 months, he continued to have worsening vision changes and vision loss, thus weekly rituximab infusions were initiated for 4 weeks in October 2022, which resulted in a moderate improvement of visual symptoms. The prednisone taper, which was initially prescribed 2 months prior, was continued for outpatient symptom management; however, his vision loss continued to worsen as seen in his monthly follow-ups. He returned in December 2022 and was admitted for further treatment of his optic neuritis. After round 2 of PLEX (5 sessions every other day) followed a week later with round 3 of HD MPD with no results, monthly tocilizumab therapy was recommended by a consulting neuroimmunologist specialist.

The patient received his first dose of tocilizumab (8 mg/kg IV) in December 2022. Ten days later, he presented to the emergency department for a 2-day onset of acute lower abdominal pain. He was taken to the operating room with concern for a ruptured appendix. In the operating room, surgeons identified purulent

**Figure.** NMO patient clinical course timeline.




*CRRT, continuous renal replacement therapy; DKA, diabetic ketoacidosis; IVIG, intravenous immunoglobulin; MPD, methylprednisolone; NMO, neuromyelitis optica; PICU, pediatric intensive care unit; PLEX, plasmapheresis; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TPN, total parenteral nutrition.*

fluid and bowel contents in the abdomen without a ruptured appendix, so they converted to an exploratory laparotomy and discovered a D4 duodenal perforation, which was repaired. Enteral medications were converted to IV forms, including prednisone, which was converted to an equipotent dose of methylprednisolone. Approximately 1 week later, in mid-January 2023, the patient experienced increased abdominal pain and distention and was unable to tolerate enteral nutrition, so he was taken back to the operating room. Another exploratory laparotomy was conducted where a D3 duodenal perforation was identified and repaired. Total parenteral nutrition (TPN) was initiated at this time. Six days later, an increase in abdominal pain and distention once again occurred and in the operating room he was found to have tissue failure at the D3 duodenal repair site, so this was once again repaired.

Following the duodenal perforations and repairs, he stabilized and subjective improvements in vision were noted by the patient and by ophthalmologic examinations. However, in late January 2023, he was found unresponsive, and a rapid response was issued. He was upgraded to the pediatric intensive care unit, intubated, and found to have massive blood loss from his abdomen and diabetic ketoacidosis. Appropriate therapies, including massive blood transfusion, vasopressors, fluids, and insulin drips, were used and an emergent bedside exploratory laparotomy was performed to identify the source of the hemorrhage and repair it. Despite medical and surgical interventions, he continued to have assessments and imaging consistent with abdominal fluid due to perforation leaks, necessitating the placement of drains. Peritoneal fluid cultures grew multiple organisms, most notably, *Aspergillus flavus,* which continued to grow and disseminate in the abdomen. The patient was placed on amphotericin intra-abdominal irrigations/beads intraoperatively, and micafungin therapy was initiated for systemic therapy to treat fungal peritonitis. Upon visual assessment, his abdomen was noted to include fat necrosis with fungal deposits throughout. The systemic antimicrobial regimen was escalated to vancomycin, cefepime, and metronidazole for extended coverage in late January 2023. A couple of months into his admission, with little clinical improvement despite multiple antimicrobial regimens (see Supplemental Table), the patient continued to experience significant decompensation and end organ failure, likely the result of the disseminated *Aspergillus*, prolonged parenteral nutrition therapy, and combined medication-related side effects. He was placed on continuous renal replacement therapy (CRRT) and a tracheostomy was performed to provide better support. However, given the patient's poor wound healing, overall immunocompromised state, ongoing concerns about duodenal leakage, and inability to tolerate enteral nutrition, his care team and family engaged in a goals-of-care discussion. It was recognized that ongoing therapies, including CRRT, ventilator support, and TPN, were causing more harm than benefit, further complicating his clinical status rather than improving his prognosis. Consequently, the focus of care shifted toward prioritizing comfort and quality of life. The patient died surrounded by his family and friends in May 2023 after 4 months of hospitalization and nearly a year of extensive therapies.

The combination of tocilizumab and prolonged, high-dose corticosteroids were the leading potential cause of GIP and subsequent invasive infection in this patient. Both the high-dose IV MPD and oral corticosteroids received over 6 months prior to tocilizumab contributed to his risk for these adverse events. The 15-year-old's fatality provides evidence of the need for interdisciplinary discussions of independent patient risk factors before the initiation of this novel drug.

## Discussion

While this case report shares some similarities to previously published reports, our patient's outcome and age are 2 key differences. Few cases mention the use of tocilizumab for pediatric NMO, but the reported results present favorable patient outcomes. In one published case, a 17-year-old female with NMO experienced no relapse in vision loss for over 36 months once initiated on monthly tocilizumab IV 8 mg/kg. However, this adolescent began tocilizumab 6 months after the initial presentation of NMO. In our patient, nearly a year passed before the initiation of tocilizumab, and prolonged, high-dose corticosteroids were used. Prednisone doses exceeding 7.5 mg per day are an established risk factor for GIP in patients receiving tocilizumab, and our patient consistently received 60 mg of prednisone or equivalent for over 5 months before tocilizumab, placing him at a higher risk for this adverse event.[7]

Another pediatric case reports successful use of monthly tocilizumab IV 8 mg/kg for refractory NMO with the latest clinical follow-up being 7 months after initiation. The success seen in this 15-year-old patient could be due to the presence of antibodies against aquaporin-4 (AQP4), a hallmark diagnostic of NMO.[8] Our patient was negative for both anti-myelin oligodendrocyte glycoprotein and anti-AQP4 antibodies, which may have contributed to the differences in clinical results. The reported patient did not experience worsening vision or show radiographic evidence of disease progression. However, our patient was unable to continue tocilizumab owing to suspected contribution to or cause of bowel perforation. The likely etiology of our patient's optic neuritis was heavily manifested in his autoimmune response after SARS-CoV-2. As the long-term effects of SARS-CoV-2 are being studied, there is an increasing association between NMOSD and the hyperactive autoimmune manifestations of the virus.[9]

A similar case report of another 15-year-old male presenting with multiple GIPs after his second infusion

of tocilizumab has been reported. These perforations occurred 8 days after this infusion, which provided a timeline similar to that of our patient.[10] We hypothesize that the delay in GIP development is related to the drug's half-life of 11 days.[11] However, this case reports only 3 months of corticosteroid therapy as compared with our patient who received a longer course. This disparity reinforces the assertion that both the dosage and duration of corticosteroid therapy likely contributed to the development of tocilizumab-induced GIP.

While the pathophysiology of GIP caused by tocilizumab is not well understood, prior case reports of this adverse event in adults have explored possible mechanisms. Tocilizumab is used for inflammatory autoimmune disease and acts by blocking the activity of interleukin-6, which decreases concentrations of vascular endothelial growth factor. Vascular endothelial growth factor assists with maintaining intestinal mucosa and immune system function. Long-term corticosteroid use, as seen in our patient, also increases the risk of GIP by decreasing the activation of inflammatory cells.[12] Providers should consider tocilizumab's ability to lower intestinal integrity in patients who are predisposed to GIP owing to corticosteroid treatment before initiation.

The diverse indications for tocilizumab, ranging from SARS-CoV-2 to NMO, necessitate careful patient selection, because underlying conditions and concurrent therapies may elevate the risk of adverse events. Identifying patients who may not be ideal candidates for tocilizumab is crucial to ensuring safe and effective use. In our patient, a previously healthy male prior to the NMO diagnosis who received the prolonged administration of high-dose corticosteroids, combined with the timing of tocilizumab administration relative to the development of GIP, strongly suggests that tocilizumab—likely in conjunction with prolonged steroid use—was a key contributor to the GIP. The perforation subsequently became infected, ultimately leading to his untimely death. Further studies are needed to identify specific risk factors that may increase the risk for serious adverse events when receiving tocilizumab for inflammatory autoimmune diseases of the eye. Furthermore, we hope our case will encourage increased reporting of adverse events associated with medication use.

## Conclusions

To our knowledge, our case represents the first report of a pediatric patient administered a single dose of tocilizumab for NMO, who experienced unusual adverse reactions linked to this medication and the effects of prolonged, high-dose corticosteroids: an invasive fungal infection and a GIP. Health care providers should carefully assess the risks and benefits of therapies on a patient-specific basis prior to initiation of the therapy. The uncommon yet severe outcome in our patient underscores the need for caution and emphasizes the significance of collaborative decision-making before initiating tocilizumab therapy.

## Article Information

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