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## Innovation for rare diseases and bioethical concerns: A thin thread between medical progress and suffering

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### Abstract

With the development of precision medicines based on small molecules, antibodies, RNAs and gene therapy, technological innovation is providing some exciting possibilities to treat the most severe genetic diseases. However, these treatments do not always lead to a cure for the disease, and there are several factors that may hinder their overall success. Patients living during a period of great medical change and innovation may benefit from these technological advances but may also just face failures, both in terms of frustrated hopes as well as suffering. In this article, we are telling the stories of three children with rare and severe disorders, who live in an age of significant medical changes, bearing the burden of difficult scientific and ethical choices. The first two cases that are suffering respectively from severe immunodeficiency and beta thalassemia have already been described in scientific journals, as well as in popular magazines. Although similar when considering the medical challenges, the two cases had opposite outcomes, which resulted in distinct ethical implications. The third case is a baby with spinal muscular atrophy, living at a time of continued innovation in the treatment of the disease. With these cases, we discuss the challenges of providing correct information and proper counseling to families and patients that are making the bumpy journey on the road of medical innovation.

**Key words:** X-severe combined immunodeficiency; Primary immunodeficiency; Beta thalassemia; Spinal muscular atrophy; Bioethics; History of medicine; Precision medicine; Genetics

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**Core tip:** Precision therapies are heralded to change the prognosis of rare and severe genetic disorders. However, the new treatments are not always curative and what can be viewed on one hand as a partial improvement,

on the other may result, at least for some patients, in prolonged suffering. During this period of change, great hopes but unpredictable outcomes can mark the lives of patients. Recalling and considering the ethical debates on historical cases can help doctors in giving the right advice to the families of patients with rare and severe disorders.

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## INTRODUCTION

The history of medicine is riddled with successes and failures with exciting innovations and untold suffering. The contrast between the hopes pinned on innovation and the prolonged suffering in real life is particularly reflected by the experience of suffering from complex and rare disorders. It has been argued that the timetable of research sadly does not fit the life expectancy of patients. Even when progress seems to make headway, we can identify at least three groups of patients: those who are too late to benefit from novel treatments, those who will witness the success of innovative therapies, and those who will journey on the bumpy ride of innovation too slowly, facing new medical problems and ethical concerns. Subjects in the third group call for attention, as their lives will be challenged by difficult choices, whether to accept the risks brought on by changes, often ignoring whether innovation will have results of improvement that are clinically relevant. Moreover, they must cope with the difficulties of obtaining novel medications, which may be offered to them following a label prescription or as part of clinical trials that can require extraordinary willingness to cooperate and sometimes are never granted marketing authorization<sup>[1-3]</sup>. Doctors will inform patients and/or their caregivers about the costs/benefits of the new treatments, based on the best expertise at any given moment. However, the partial medical knowledge and highly heterogeneous progression of the disease in addition to the response to treatments may hinder a reliable prediction of the disease outcome. This is particularly true for those patients with severe rare diseases. Even if regulatory agencies established robust rules to protect patients, their journey across major changes in medical knowledge and practice can be full of unforeseen difficulties.

In the first part of this article we mention two stories from the past, which both raised bioethical concerns and received media attention. For both cases, significant advances in medical care were paralleled by the personal stories of patients, who lived during remarkable scientific innovation. During this period, these patients went through moments of great hope and painful ad-

versity. In retrospect, our judgment concerning their cases cannot be impartial to the respective clinical outcomes and the social achievements during that time, in particular concerning birth control, prenatal genetic testing, and facing the prospect of death. However, it is not our intention to judge, but just to remember how difficult it can be to make the right choice. Even if each disease is considered in its own right, in the second part of the article we discuss how these lessons learnt from history can help us to cope with new challenges, such as the medical innovation that is on its way regarding spinal muscular atrophy (SMA).

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## DISCUSSION CASE #1

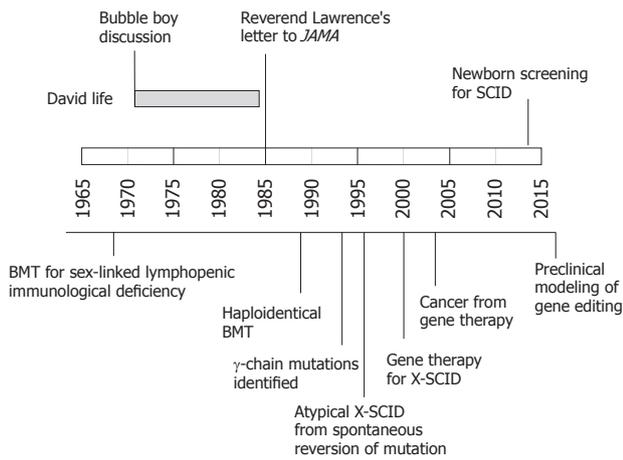
### *The case*

#### **These are the days of miracle and wonder, Simon**

**P:** The bubble boy: Immunodeficiencies at the time of molecular immunology. The story of David Vetter, also known as "the bubble boy", has been described in detail elsewhere, both in scientific manuscripts and across some of the world's magazines, as well as in a movie (*The Boy in the Plastic Bubble*, 1976, by Douglas Day Stewart) and in a documentary (*PBS American Experience*, 2006)<sup>[4-6]</sup>. The life of the boy inside a plastic bubble was at the same time a theme for scientific and ethical debate and also a popular real show, probably offering a much more cheerful portrait than in reality.

David's parents had their first son in 1970. Unfortunately, he died of severe combined immunodeficiency (SCID). Since there was no family history for immunodeficiency and the molecular defects underlying SCID were still unknown, it was impossible to predict the exact risk of familial recurrence of the disease. However, doctors informed the Vettters that, if they would have another child with SCID, the newborn could be delivered by cesarean section and immediately placed in a sterile environment by means of a plastic "isolator" that would protect him from infections until a cure was found. Being animated by a catholic sense of procreation and a fair trust in the doctors, the Vettters soon had a second boy, David, who was also diagnosed with SCID. The isolation of David in a sterile environment was made possible due to a dedicated research project at the Children Hospital in Houston. Despite great efforts to create a domestic environment in the bubble, the life inside could not have been so comfortable, not only because of the difficulty to interact with others, but also for the constant noise of the bubble's blower motors, turning the room into a scientific laboratory. As a research project, it led to several scientific publications, but also to ethical debates<sup>[4,5,7-12]</sup>.

It is difficult to try and interpret David's story only from indirect data. However, much of his life was dominated by the conflict between his natural curiosity about the world and the fear of microbes, which was taught to him to decrease his desire to come out of the bubble. When he was six years old, National Aeronautics and Space Administration (NASA) made him a special spacesuit coat to allow for safe walking outside of the



1971	Born by cesarean section in a germ-free environment at the Texas Children's Hospital and placed in a sterile plastic chamber
1974	Plastic bubble built at Vetter's home
1975	Bioethical conference on the David's case
1977	NASA constructed a special space suit to allow him to walk outside
1978	First psychological crisis
1983	HLA-mismatched bone marrow transplantation from the older sister
1984	He died from EBV-related Burkitt's lymphoma

**Figure 1** The timeline of David's life paralleled by the most significant advances in understanding and treating X-severe combined immunodeficiency. SCID: Severe combined immunodeficiency; BMT: Bone marrow transplantation; HLA: Histocompatibility leukocyte antigen; EBV: Epstein-Barr virus; NASA: National Aeronautics and Space Administration.

bubble (the so called "Mobile Biological Isolation System"). His reluctance to use this device only after several walks reflects the contrast between his fears and his dreams. As he grew older, he would live through even more conflicts. He soon became aware of how his life was different from his peers and how senseless it was to study things that he could not experience in reality. It does not come as a surprise that he started developing unbearable sadness and depression despite the support from Mary Murphy, a psychologist dedicated to the prevention and treatment of emotional crises. Murphy wrote a concerning tale about her experience with the boy, which was never published due to the contrariety of the parents and the medical staff. She also wrote a scientific manuscript about David's psychological development<sup>[13]</sup>.

At the age of 12 years, due to the untenable life conditions and recent medical advances, David underwent histocompatibility leukocyte antigen (HLA)-mismatched bone marrow transplantation from his older sister. Unfortunately, he developed Burkitt's lymphoma and died a few months later in February 1984. His death was followed by a scientific and ethical debate with several contributions in *JAMA*<sup>[14-16]</sup>. Great attention was given to a letter from the Reverend Raymond J Lawrence, the chaplain of the Houston Children Hospital, who manifested

his disappointment in the case, criticizing the excessive trust in science that had led a boy to be conceived "for research", not considering the potential damages that a possible medical failure could cause to him<sup>[14]</sup>.

It will remain a matter for debate whether the case of David represents more of a triumph for technology or an error in estimating the power of medicine. Even if ethical issues were discussed at a conference in 1975, years before the death of the boy, a different outcome after transplantation could probably have influenced everyone's judgment. What remains true, apart from any ethical considerations on the case, is the fact that David lived through a period of great changes, both in medical science and in bioethics.

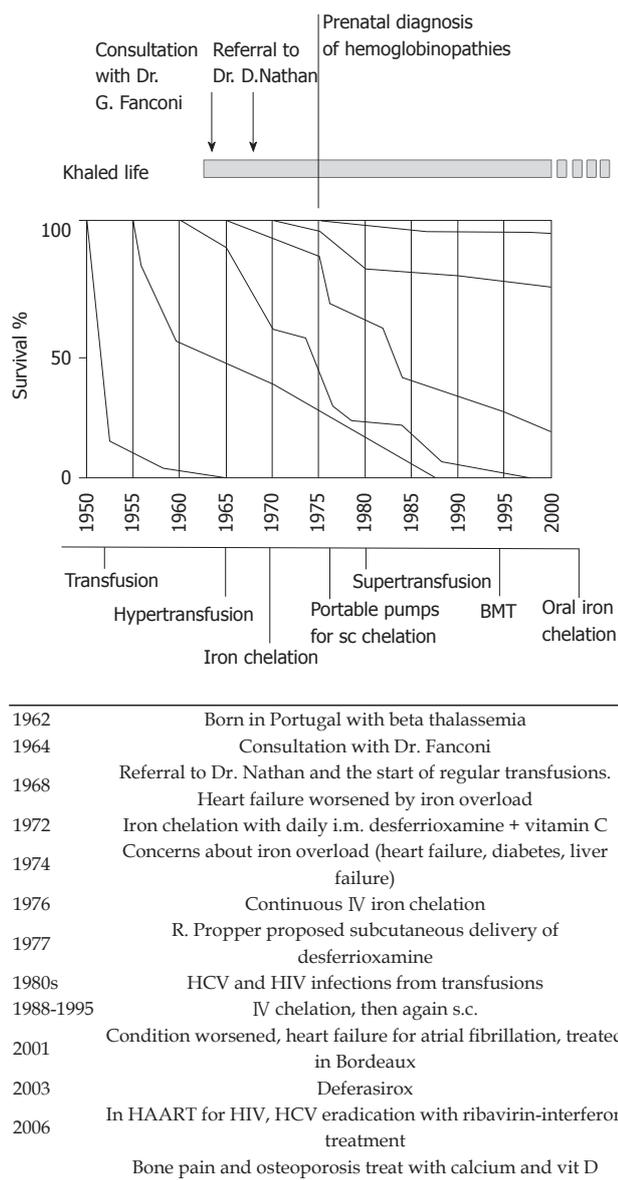
**The context**

This story is well placed at the beginning of a scientific revolution that witnessed memorable breakthroughs in the field of immunology. Some of his doctors even envisaged the possibility that, once the causative gene would be identified (and it would only be identified in 1993)<sup>[17]</sup> the disease could be cured with gene therapy. In Figure 1, the life of David is paralleled by a brief history of knowledge on X-SCID. Only a few babies, before David, survived SCID due to bone marrow transplantation from matched related or unrelated donors<sup>[18-21]</sup>. More recently, several reports showed that the outcome of hematopoietic stem cell transplantation has greatly improved in the last two decades. The early diagnosis, thanks to neonatal screening or based on family history, is a major determinant of this success, allowing the procedure to be performed before the development of chronic infections, which are the greatest threat to the patients' survival<sup>[22,23]</sup>. Hematopoietic stem cell protocols have been optimized in such a way that matched unrelated donors are now considered a suitable source of stem cells, with a rate of success not much lower than for HLA-matched siblings. Gene therapy was accomplished at the turn of the third millennium, and X-SCID was one of the first applications for this technology<sup>[24]</sup>. Indeed, the observation of attenuated X-SCID phenotypes in subjects who developed T cell clones with spontaneous reversion of the genetic mutation highlighted a favorable proliferative fitness of corrected cells and predicted the success of gene therapy<sup>[25]</sup>. However, initial attempts of gene therapy were burdened by the development of leukemia due to insertional activation of the LMO2 oncogene<sup>[26]</sup>. The simultaneous improvements in the outcome of bone marrow transplantation hindered further applications of gene therapy for X-SCID until recent advances of the development of safer vectors and of the preclinical development of gene editing approaches<sup>[27,28]</sup>.

**CASE DISCUSSION #2**

**The case**

**You are soul's unbreakable, Muse:** The history of Khaled, an "immortal" boy. This is the history of a boy born in 1962 who was affected by severe anemia due



**Figure 2** The timeline of Khaled's life paralleled by the most significant advances in understanding and treating Beta thalassemia major. BMT: Bone marrow transplantation; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HAART: Highly active antiretroviral therapy.

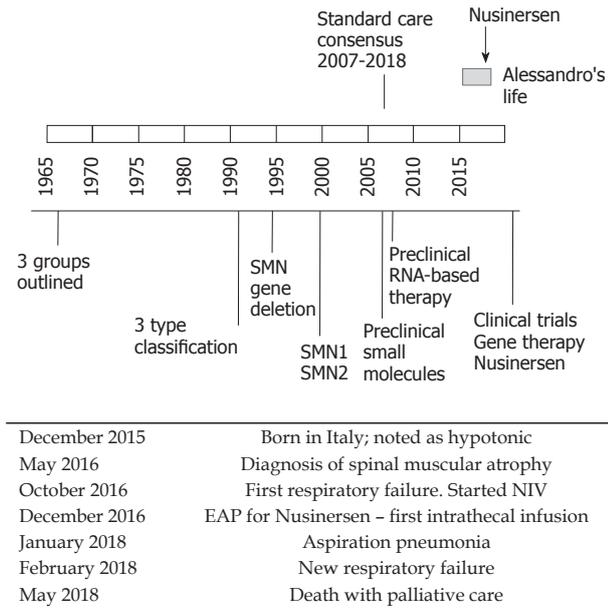
to beta thalassemia<sup>[29,30]</sup>. His parents were Jewish and of Syrian and Iranian lineage living in Portugal. At that time, thalassemia major was invariably fatal in infancy. Subjects with the most severe form of thalassemia had only transient benefits from transfusions, which were quickly outweighed by the consequences of iron overload. Indeed, when Khaled's parents sought the opinion of the foremost pediatric hematologist in Europe, Guido Fanconi at the Kinderspital in Zurich, he explained to them that there was no recommendation on treating the boy with transfusions. Blood transfusions could allow him to survive several years longer but there would be complications and suffering from enriched iron overload. There was also the possibility that he could have had a milder form of the disease than was first thought,

and therefore he could survive without transfusions. Dr. Fanconi gave a well thought out opinion, following the best of the available expertise, based both on science and humanity. Four years later, the boy had survived, albeit with severe anemia, hepatosplenomegaly, gross bone deformities and recurrent fractures. Thus, the parents decided to seek the attention of David G Nathan, a hematologist in Boston, who was making significant progress with the treatment of thalassemia. As shown in Figure 2, patients' survival was slowly increasing in the cohort of patients born in the late 1960s. However, there was no medication available to efficiently reduce iron overload, and thus it was hard to predict possible changes in the natural history of the disease in subsequent years. When Dr. Nathan decided to start regular transfusions, the increasing iron overload contributed to the possibility of heart failure making the treatment even more challenging. Fortunately, iron chelation was entering clinical protocols for thalassemia major, even if intramuscular administration of the drug allowed insufficient urinary excretion of the metal<sup>[31,32]</sup>. Great advances were achieved with continuous intravenous administration, and in 1977 subcutaneous delivery of the medication was implemented. Patients were required to stay at the hospital for long periods until portable infusion pumps were designed and became available. As shown in Figure 2, Khaled's life paralleled the most significant advances in the treatment of the disease, witnessed by a continuous improvement in life expectancy in subsequent generations. Dr. Nathan<sup>[29]</sup> characterized this story in a beautiful book, showing how the life of his patient paralleled the history of medical successes and defeats (like viral infections) in thalassemia. An update of this story can be read in the Harvard magazine<sup>[30]</sup>.

**The context**

The graph in Figure 2 summarizes the experience of Vullo and his collaborators, in Ferrara Italy, but it can also fit in the experience of other groups dealing with this disease<sup>[33]</sup>. Indeed, most pediatricians caring for patients with thalassemia experienced these exciting changes. Only an effective super-transfusion iron chelation regimen can completely suppress the patient's hemopoiesis and prevent the complex cascade typical of the disease: inhibition of hemopoiesis prevented both anemia and bone deformities; iron chelation prevented organ damage to the heart, liver and endocrine glands<sup>[34-38]</sup>.

Today the burden of beta thalassemia has been greatly reduced because of several factors including careful identification of the carriers, birth prevention of newborns with beta thalassemia major, early treatment of patients with blood transfusion and iron chelators, in some cases with bone marrow transplantation, and gene therapy<sup>[39]</sup>. Fortunately, the incidence of thalassemia major has decreased in countries with a higher prevalence of heterozygous individuals due to public information campaigns, population screenings, genetic counseling, and prenatal diagnosis, either voluntary or through



**Figure 3** The timeline of Alessandro's life paralleled by the most significant advances in understanding and treating spinal muscular atrophy 1. NIV: Non-invasive ventilation; EAP: Expanded access program.

institutional basis<sup>[40,41]</sup>.

### CASE DISCUSSION #3

#### The case

**“How many roads must a man walk down before you call him a man?” Dylan B:** A case of SMA at the time of a major medical progress. The story of Alessandro begins on a night in December 2015 in Italy. Following reduced fetal movements and the mother's hypertension, he was born prematurely at 32 wk of gestation. After birth, severe hypotonia was noted. Alessandro spent his first two months of life in a neonatal intensive care unit with a breathing machine and a feeding tube to sustain his vital functions. After a hard and complicated time, he was discharged with persisting hypotonia. He never achieved enough strength to sustain his head and his parents became aware that something was wrong. At 6 mo old, he was diagnosed with SMA. At that time, no cure for SMA was available and the treatment was based on respiratory and feeding assistance (standard care, see Figure 3). At 7 mo old, the parents took part in a special program on how to assist children with SMA and learned how to manage the ordinary and extraordinary practice of their child's daily life. At 10 mo old, Alessandro had his first breathing failure and a non-invasive ventilation (NIV) was started. This experience led his parents to understand the meaning of palliative care. They refused aggressive treatment and tracheotomy. However, in the same month Nusinersen, a new and promising drug for SMA became available, and the parents entered into the expanded access program (EAP) for this drug. At 12 mo old, Alessandro received the first intrathecal drug

infusion. After the fourth infusion, positive results became evident: small limb movements reappeared, NIV was reduced from 18 h/d to 10 h/d, and the ability to swallow was effectively increased. Nusinersen infusion, a lifelong treatment, was continued for another year and albeit further small improvements were noticed. The child also took part in an advertising campaign, which aimed to gather funds for research in SMA. In January 2018, at 25 mo old, Alessandro had aspiration pneumonia. He was hospitalized for three weeks, and he lost the strength and confidence gained in the previous year. NIV was necessarily increased to 16 h/d, and a percutaneous gastrostomy was proposed to reduce the stress of eating. After 15 d, the child was hospitalized again because of a new respiratory failure. Alessandro and his parents' state of mind completely changed in the last two months: they faced the prospect of death as they realized that SMA was getting worse despite Nusinersen. The drug was able to improve the quality of life, but it was not a cure. The last respiratory failure was crucial in the parents' choice. With great pain and fear, but also with the peacefulness of having accepted the fatal course of the disease, the parents chose palliative care. A few days later Alessandro died without pain. His mother said, “I never allowed a cold to tear away my son, but I also never asked him to win the Olympic games just for the fear of living with torment. Love also means letting it go”.

#### The context

SMA is the most common genetic cause of infant mortality in developed countries. The first International Consensus Statement for Standard of Care in SMA in 2007 has represented a fundamental milestone in the history of SMA<sup>[42]</sup>. In fact, the large variation in the disease phenotype of SMA hinders a reliable prediction of the natural course of the disease in each case. Moreover, the existence of relevant differences in clinical care at different hospitals is a serious challenge for families in making a balanced decision. Until recent developments, almost all subjects with SMA1 died in their first year of life due to respiratory failure and infections. SMA does not affect cognitive development, making it even more painful when considering the conflict in children between their growing interests and their limited abilities. Death usually occurs after prolonged agonies in children receiving quite aggressive care with artificial nutrition and ventilation. Thus, in SMA1, this point has been and still is critical to determine the threshold for choosing between palliative care and intervention, considering caregivers beliefs and opinions, as well as their capacity to shoulder the burden of the disease<sup>[43]</sup>. Parents/caregivers must receive complete information on the possible treatment options. Facing these ethical problems is part of the experience of most pediatricians as described in the example by Gray and his collaborators<sup>[44]</sup>. To make matters even more difficult, we are now living in a period of significant medical advances for the treatment of SMA, thus the threshold for decision-making may change

accordingly within the lifespan of patients<sup>[45]</sup>. For example, pharmacologic treatment with Nusinersen may improve motor skills and prolong life expectancy, but in the most severe cases it is not clear if these effects can represent a desirable benefit or therapeutic persecution. Sometimes it may just be impossible to know. Moreover, the launch of Nusinersen for SMA raised several medical concerns<sup>[46]</sup>. First, the primary outcome of the ENDEAR trial, which led to the authorization of the drug, was changed while the study was ongoing<sup>[47,48]</sup>. Even though the overall survival, free of permanent mechanical ventilation, was the original primary outcome, this was shifted during the trial to “motor milestone response”, which is defined as “more milestones improved than worsened” (considering the following milestones from the Hammersmith Infant Neurological Examination: kicking, head control, rolling, sitting, crawling, standing, and walking). The result of this change was the approval of the drug based on marginal albeit significant improvements in motor function. Based on the result of the ENDEAR trial and on other uncontrolled trials, Nusinersen was granted marketing authority for all types of SMA. However, the achievements shown in ENDEAR were not as clearly proven for all types of the disease and at any age<sup>[46]</sup>. Secondly, whilst the proof of efficacy of the drug was obtained in subjects with SMA1 who were younger than 6 mo old at the time Nusinersen was first administered, the drug had been approved for all types of the disease. Thirdly, the extremely high costs of the treatment risked making it not equitably distributable. Moreover, it is even debatable if the same amount of money could not have been used in better ways to improve the care for patients. Finally, the most serious concern is that Nusinersen does not represent a cure and in some cases may be too risky. Paradoxically, the availability of Nusinersen may have an unpredictable impact on decisions about prenatal screening. It is of note that the availability of iron chelators, increasing chronicity, and healthcare costs in beta thalassemia had a role in driving prevention programs in Cyprus, where the disease is prevalent<sup>[49]</sup>. Similarly, it could be expected that the availability of Nusinersen may increase screening programs for SMA. Some would argue that Nusinersen may increase patients’ survival to allow for better care (perhaps gene therapy) in the near future. However there is no reliable prediction about this. Thus, we must recognize that children with SMA are living today during major periods of change, like in other stories described in this article<sup>[50]</sup>.

## CONCLUSION

Making the best choice during periods of mounting medical advances among prenatal screening, palliative care, and aggressive treatment can be difficult when dealing with severe diseases. On the one hand, medical progress is increasing the probability of survival for children with severe genetic disorders; on the other, genetic screenings are offering a way to reduce the birth of newborns with

relatively common severe disorders like cystic fibrosis, SMA, and thalassemia<sup>[51,52]</sup>. It may be difficult to find the correct direction between full fruition of life and the maintenance of some vital function with unbearable suffering. Parents’ ethical, cultural, and religious feelings should be considered together with the best medical evidence to elaborate shared bioethical opinions in each case.

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## Clinical features of acute kidney injury in patients with Kawasaki disease

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### Abstract

Although acute kidney injury (AKI) is a common complication in hospitalized children, AKI has rarely been reported in patients with Kawasaki disease (KD). Herein, we review the clinical trajectories of AKI in patients with KD. A total

of 39 patients with KD who developed AKI have been reported in 28 publications as case reports. The causes of AKI include prerenal AKI associated with acute heart failure (AHF), intrinsic AKI caused by tubulointerstitial nephritis (TIN), acute nephritic syndrome (ANS), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, rhabdomyolysis, and KD shock syndrome (KDSS). Six of the 39 patients (15.4%) underwent renal replacement therapy. While AHF and multiple organ dysfunction syndrome developed in 41% and 68% of KD patients with AKI, respectively, all patients recovered without any renal sequelae. Although the precise pathogenic mechanism underlying the development of AKI in patients with KD is unknown, several possible mechanisms have been proposed, including T-cell-mediated immunologic abnormalities for TIN, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune complex-mediated nephropathy and ASN, and capillary leak and an increased release of cytokines with myocardial dysfunction for KDSS.

**Key words:** Kawasaki disease; Acute kidney injury; Kidney involvement; Multiple organ dysfunction syndrome

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**Core tip:** Acute kidney injury (AKI) has rarely been reported in patients with Kawasaki disease (KD). We review the clinical characteristics of AKI in patients with KD and show that AKI is caused by a number of pathologic changes induced by KD. Patients with KD and AKI had good outcomes, despite the developed of multiple organ dysfunction syndrome. The possible mechanisms underlying the development of AKI in KD include T-cell-mediated immunologic abnormalities, renal and glomerular endothelial injury resulted from vasculitis, immune complex-mediated kidney injury, and capillary leak and the increased release of cytokines with myocardial dysfunction.

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## INTRODUCTION

Kawasaki disease (KD) is a systemic vasculitis that occurs mainly in infants and children<sup>[1]</sup>. Although clinical and epidemiologic studies suggest an infectious etiology, the causative agent has yet to be determined<sup>[2]</sup>. Recent studies have suggested that an immunologic reaction is induced in genetically-susceptible hosts upon exposure to the KD trigger<sup>[2]</sup>. Because KD is a systemic vasculitis, KD can involve multiple organs and tissues, including the kidneys<sup>[3]</sup>.

Kidney complications in KD include pyuria, trace proteinuria, prerenal acute kidney injury (AKI), intrinsic AKI resulted from tubulointerstitial nephritis (TIN), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, intrinsic AKI associated with KD shock syndrome (KDSS), acute nephritic syndrome (ANS), nephrotic syndrome (NS), and renal tubular abnormalities<sup>[4]</sup>. Although patients with KD often present with sterile pyuria and trace proteinuria, other kidney complications in KD are uncommon<sup>[4]</sup>; however, several laboratory and imaging studies have shown that a number of patients with KD develop subclinical kidney injury<sup>[5,6]</sup>.

AKI is a common complication in hospitalized children<sup>[7]</sup>. Recent studies have shown that AKI developed in 26.9% of children and young adults admitted to the intensive care unit (ICU)<sup>[8]</sup>, and in at least 5% of non-critically ill hospitalized children and young adults<sup>[9]</sup>. Because AKI is associated with poor outcomes, including a high mortality rate and long-term morbidity<sup>[7,10]</sup>, it is important to establish the causes and clinical features of hospitalized children with AKI, as well as patients with KD. The clinical trajectories of AKI in patients with KD are the subject of this mini-review.

We conducted a computerized search of the English, French, and Spanish literature using the PubMed database with a search engine and the Japanese literature using the Japan Medical Abstract Society database with a search engine from January 1967 through April 2018. The search used a combination of the following terms: "Kawasaki disease" with "acute kidney injury" or with "acute renal failure". Also, a direct search of cited references was conducted. The clinical criteria in the 2004 American Heart Association/American Academy of Pediatrics guidelines were used to diagnose KD<sup>[11]</sup>. AKI is usually defined as serum creatinine level elevation  $\geq 1.5$  times the baseline level, according to Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury<sup>[12]</sup>. Because the baseline level of serum creatinine was not documented in most of the patients searched in this study, AKI was defined as a

serum creatinine level  $\geq 1.5$  times the upper limit of the normal age-specific serum creatinine reference level<sup>[13,14]</sup>. Studies which had insufficient clinical information for each patient were excluded from detailed analysis of the clinical manifestations of KD patients with AKI.

## PREVALENCE OF AKI IN PATIENTS WITH KD

Chuang *et al*<sup>[13]</sup> studied the clinical characteristics and laboratory data of 336 Taiwanese patients with KD, including serum creatinine levels, and reported that 28% of the patients with KD developed AKI. Moreover, young age and elevated alanine transaminase level were reported to be the main factors associated with AKI. Based on our review of the clinical and laboratory data of 249 Japanese children with KD, however, no patients developed AKI<sup>[15]</sup>. Although it is not clear why the two reports yielded a different prevalence for AKI in patients with KD, it is possible that differences in disease severity influenced the results<sup>[15]</sup>.

## EPIDEMIOLOGY

Thirty-nine patients with KD who developed AKI have been reported in 28 publications as case reports<sup>[16-43]</sup>. The median age was 4.8 years (range, 3 mo-to-45 years). Twenty-seven patients were male (male-to-female ratio, 2.07:1). Thirty-two patients developed complete KD, while 7 patients had incomplete KD.

## CAUSES OF AKI

The causes of AKI are usually divided into the following three pathophysiologic categories: prerenal AKI, which is characterized by effective hypoperfusion of the kidneys and a lack of parenchymal damage to the kidney; intrinsic AKI, which involves renal parenchymal damage; and postrenal AKI, which is associated with acute obstruction of the urinary tract<sup>[44]</sup>. In patients with KD, prerenal AKI associated with acute heart failure (AHF)<sup>[16,17]</sup> and intrinsic AKI have been reported. The causes of intrinsic AKI in KD include TIN<sup>[18-21]</sup>, ANS<sup>[22-24]</sup>, HUS<sup>[25-27]</sup>, immune complex-mediated nephropathy<sup>[28]</sup>, rhabdomyolysis<sup>[29]</sup>, and KDSS<sup>[30-34]</sup> (Table 1); however, because only 8 of the reported KD patients with AKI underwent renal biopsies, the etiology of AKI was unknown in 25% of the patients<sup>[35-43]</sup>.

## CLINICAL MANIFESTATIONS

Oliguria, edema, hypotension, and hypertension occurred in 62% (18/29), 31% (2/29), 41% (16/39) and 15.4% (6/39) of the KD patients, respectively, and AHF developed in 41% (16/39) of the KD patients. Based on the Goldstein diagnostic criteria, 68.4% of patients had multiple organ dysfunction syndrome (MODS)<sup>[45]</sup>, and the median number of affected organs was 2 (range, 1-5).

**Table 1 Causes of acute kidney injury in patients with Kawasaki disease**

Cause	N
1 Prerenal AKI associated with acute heart failure	2
2 Intrinsic AKI	
Tubulointerstitial nephritis	4
Acute nephritic syndrome	3
Hemolytic uremic syndrome	3
Immune complex-mediated nephritis	1
Rhabdomyolysis	1
Kawasaki disease shock syndrome	14
Undetermined etiology	11

AKI: Acute kidney injury.

The dysfunctional systems included the cardiovascular system in 41% (16/39) of the patients, the respiratory system in 10.2% (4/39), the nervous system in 25.6% (10/39), the hematologic system in 5.1% (2/39), and the hepatobiliary system in 33.3% (13/39).

The median blood urea nitrogen level was 58 mg/dL (range, 8-194 mg/dL), and the median serum creatinine level was 2.2 mg/dL (range, 0.5-7.43 mg/dL). Sixteen of 20 patients (80%) had hyponatremia (serum sodium < 135 mEq/L), 82.1% had proteinuria, 46.4% (13/28) had hematuria, and 73.9% (17/23) had pyuria. Three patients with KDSS developed NS, and 3 patients with ANS had macroscopic hematuria.

Only 8 patients underwent renal biopsies, which revealed TIN in 4 patients, ATN in 2, immune complex-mediated nephropathy in 1, and minor abnormalities in 1. Thirty of the 39 patients (76.9%) underwent intravenous immunoglobulin (IVIG) therapy. IVIG therapy was effective in 73.3% (22/30) of the patients, while 26.7% (8/30) were IVIG-resistant. Six of the 39 patients (15.4%) had renal replacement therapy, which included hemodialysis in 4 patients, continuous hemodialysis in 1, and peritoneal dialysis in 1.

All patients recovered from AKI without any renal sequelae. Although transient coronary artery dilatation occurred in 28.2% (11/39) of the patients, coronary artery aneurysms (CAAs) developed in 5.1% (2/39).

### Prerenal AKI

Two patients with KD who developed prerenal AKI have been reported. Senzaki *et al*<sup>[16]</sup> reported an 8-year-old boy with KD who developed AHF and AKI. The results of the fractional excretion of sodium (0.04%), the renal failure index (0.02), the urine-to-plasma creatinine ratio (54), and the urine-to-plasma osmolality ratio (1.7) were consistent with prerenal AKI. Adachi described a 2-year-old girl with KD who developed prerenal AKI caused by hypovolemia due to gastrointestinal losses and AHF<sup>[17]</sup>. An intravenous fluid infusion and IVIG therapy resolved AKI following improvement of AHF in both patients, probably due to correction of hypovolemia and myocardial dysfunction, respectively.

AHF causes renal hypoperfusion due to decreased cardiac output<sup>[44]</sup>. In addition, KD is associated with

hypovolemia due to decreased oral intake, gastrointestinal losses, or third spacing resulting from increased vascular permeability<sup>[16]</sup>. Therefore, both hypovolemia and AHF may have central roles in the development of prerenal AKI in patients with KD.

### Intrinsic AKI

**TIN:** AKI due to TIN has been reported in 5 patients with KD. None of the patients had a *Yersinia pseudotuberculosis* infection<sup>[46]</sup>. Veiga *et al*<sup>[18]</sup> reported a 2-year-old boy with KD who developed AKI based on a renal biopsy, which showed diffuse interstitial infiltration of mononuclear and polymorphonuclear leukocytes. The patient was treated with IVIG, oral aspirin, fluid restriction, and furosemide, and recovered without any untoward sequelae. Kawamura<sup>[19]</sup> reported a 9-year-old girl with KD who developed AKI based on a renal biopsy, which showed mild interstitial mononuclear cell infiltration. The patient underwent hemodialysis and recovered without any renal sequelae. Ashida *et al*<sup>[20]</sup> reported a 5-year-old boy with KD who developed AKI based on a renal biopsy, which revealed interstitial infiltration of mononuclear cells. After fluid restriction and IVIG therapy, the boy recovered without sequelae. Bonany *et al*<sup>[21]</sup> reported an 8-year-old boy with KD who developed AKI and NS based on a renal biopsy, which showed TIN and acute tubular necrosis; the patient recovered with supportive care alone.

TIN is an immune-mediated cause of AKI that is characterized by the presence of an inflammatory cell infiltrate in the interstitium of the kidney<sup>[47]</sup>. Although acute TIN is largely due to medications, autoimmune diseases are associated with acute TIN, including anti-tubular basement membrane disease, TIN with uveitis, and KD<sup>[48]</sup>. Although the pathogenesis underlying TIN has not been completely described, T cell activation and the resultant cytokine and protease activity may play central roles in TIN. Because T cell activation and extensive cytokine release also occur in KD<sup>[1,2]</sup>, these immunologic abnormalities may cause acute TIN in some patients with KD.

**ANS:** AKI due to ANS has been reported in 3 patients with KD. Suzue *et al*<sup>[22]</sup> reported a 5-mo-old boy with KD who developed AKI due to ANS 2 wk after IVIG therapy with a transient decrease in serum C3 and C4 levels. The patient recovered with supportive care alone. Yoshida *et al*<sup>[23]</sup> reported a 3-mo-old girl with KD who developed AHF and AKI due to ANS 6 d after IVIG therapy with a transient decrease in serum C3 and C4 levels. While the pathogenesis underlying the development of ANS in these patients with KD was not established, an immune complex-mediated mechanism was suspected because both patients had transient hypocomplementemia following IVIG therapy.

In contrast, Motoyama *et al*<sup>[24]</sup> reported a 6-year-old boy with ANS and AKI who subsequently developed KD. The patient was administered intravenous corti-

costeroids and oral aspirin and recovered without any sequelae.

**HUS:** AKI due to HUS has been reported in 3 patients with KD. Ferriero and Wolfsdorf<sup>[25]</sup> reported a 2-year-old girl with KD who developed AKI and metabolic encephalopathy due to HUS. She recovered with supportive care alone<sup>[25]</sup>. Heldrich *et al*<sup>[26]</sup> reported a 3-year-old girl with KD who developed AKI due to HUS and Henoch-Schönlein purpura, which required adjustment to therapy. Saviour *et al*<sup>[27]</sup> reported a 2-year-old boy with KD who developed AKI due to HUS. The patient underwent IVIG therapy and supportive management of fluids and electrolytes. She recovered without any sequelae.

With renal biopsy findings, the pathogenesis of HUS in patients with KD cannot be ascertained; however, it is possible that vasculitis-associated KD may involve the kidney causing injury to the renal and glomerular endothelium, thus leading to HUS<sup>[25]</sup>.

**Immune complex-mediated nephropathy:** Nagamatsu *et al*<sup>[28]</sup> reported a 3-year-old boy with KD who developed AKI. The patient was treated with IVIG, dopamine, and furosemide. Electron microscopy of a renal biopsy specimen showed electron-dense deposits in the subepithelial spaces and podocytes, which suggested the possibility of glomerular derangement by immune complexes.

**Rhabdomyolysis:** Sevin *et al*<sup>[29]</sup> reported a 10-year-old girl with KD who developed AKI due to rhabdomyolysis that was possibly caused by hyperthermia. A renal biopsy showed renal tubular necrosis without glomerular or vascular changes<sup>[29]</sup>. The patient recovered from AKI with IVIG and supportive care alone.

**KDSS:** KDSS is a condition characterized by systolic hypotension or clinical signs of poor perfusion in patients with KD<sup>[49,50]</sup>. Although the pathogenesis underlying KDSS is unknown, intensive vasculitis with capillary leak and hypercytokinemia with myocardial dysfunction may cause KDSS<sup>[49-51]</sup>.

Mac Ardle *et al*<sup>[30]</sup> reported a 2-year-old boy with KDSS who developed encephalopathy, respiratory failure and AKI. A renal biopsy showed normal glomeruli and a patchy immune-type infiltrate consisting of plasma cells and eosinophils, with evidence of recovering acute tubular necrosis. The patient received an intravenous fluid infusion, underwent peritoneal dialysis, and was mechanically ventilated. The boy recovered with mild neurologic sequelae. Nakanishi *et al*<sup>[31]</sup> reported a 12-year-old boy with KDSS who developed AHF, a coagulopathy, and AKI. A renal biopsy showed no glomerular or tubular abnormalities. The patient recovered with IVIG, hemodialysis, and the intravenous administration of catecholamines. An 11-year-old girl with KDSS who developed AKI and AHF due to myocarditis was reported<sup>[32]</sup>. The patient was mechanically ventilated,

and received a diuretic intravenously, and IVIG therapy. She recovered but had CAAs. Umei *et al*<sup>[33]</sup> reported a 12-year-old boy with KDSS who developed AHF, hepatic dysfunction, a coagulopathy, and AKI. The patient was treated with IVIG, plasma exchange, continuous hemodialysis, and the intravenous administration of catecholamines. He recovered without any sequelae. Gatterre *et al*<sup>[34]</sup> studied 11 patients with KDSS and reported that 10 developed AKI. Nine of the patients had proteinuria, 3 of whom exhibited NS. All of the patients underwent IVIG therapy and recovered without sequelae.

**Undetermined etiologies:** Eleven patients with AKI of unknown etiologies have been reported. Yamawaki *et al*<sup>[35]</sup> reported a 5-year-old boy with KD who developed oliguric AKI. The patient underwent hemodialysis and recovered without any sequelae. Nardi *et al*<sup>[36]</sup> reported a 6-year-old girl with KD who developed oliguric AKI and hepatic dysfunction. The patient recovered with supportive care alone. Lande *et al*<sup>[37]</sup> reported a 3-year-old girl with KD who developed oliguric AKI. The patient received IVIG and underwent hemodialysis. She recovered without any sequelae. Ashida *et al*<sup>[20]</sup> reported a 3-year-old boy with KD who developed AKI. He was treated with IVIG and recovered without any sequelae. El Karoui *et al*<sup>[38]</sup> reported a 45-year-old man with adult-onset KD who developed AKI. He was treated with IVIG, which resulted in rapid improvement and recovery of normal renal function. Nandi and Mondal<sup>[39]</sup> reported a 4-year-old boy with KD who developed oliguric AKI. The patient recovered with supportive care alone. Keeswijk and Walle<sup>[40,41]</sup> reported a 2-year-old boy with KD who developed oliguric AKI. The patient recovered completely with IVIG therapy, fluid restriction, and a diuretic. Tiewsoh *et al*<sup>[42]</sup> reported 3 boys with incomplete KD who developed AKI. All of the patients were treated with IVIG and recovered without any sequelae. Martínez Vázquez *et al*<sup>[43]</sup> reported a 9-year-old girl with KD who developed oliguric AKI and cholestasis. The patient was treated with IVIG and intravenous pulses of methylprednisolone, which led to an improvement in the AKI and clinical features of KD, but she had CAAs.

## THERAPEUTIC STRATEGIES TO KD PATIENTS WITH AKI

Treatment of KD patients with prerenal AKI and AHF consists of appropriate restoration of the normal circulating blood volume, heart function support<sup>[44]</sup>, and specific therapy for KD<sup>[44]</sup>. Among KD patients with intrinsic AKI, renal damage results from vasculitis of the renal arteries, or T cell- or B cell-mediated immunoregulatory abnormalities caused by KD. Therefore, treatments adapted to the severity of KD can improve AKI in addition to supportive therapies to ameliorate derangements of fluid and electrolyte homeostasis, which include fluid restriction, diuretic usage and renal replacement therapy<sup>[10,44]</sup>.

## CONCLUSION

AKI in patients with KD is uncommon and includes the following conditions: prerenal AKI; intrinsic AKI caused by TIN; ANS; HUS; immune complex-mediated nephropathy; rhabdomyolysis; KDSS; and undetermined etiologies.

Although the pathogenic mechanism underlying renal involvement in patients with KD who develop AKI is unknown, several possible mechanisms have been proposed, which include T-cell-mediated immunologic abnormalities for TIN, muscle injury caused by hyperthermia for rhabdomyolysis, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune-complex mediated nephropathy and ANS, and capillary leak and hypercytokinemia with myocardial dysfunction induced by intensive vasculitis for KDSS.

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