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Addressing the Microvillus Inclusion Disease Knowledge Gap: A Comprehensive Case Analysis

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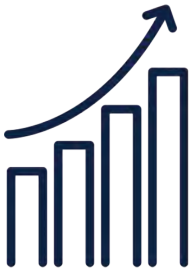
Abstract:

Many children affected by the genetic intestinal disorder known as microvillus inclusion disease (MVID) may not live to see their third birthday. Given MVID's rarity, it can be difficult for doctors, researchers, and parents confronted with the devastating disease to locate necessary data related to the disorder, presenting challenges with research, diagnosis, and the development of treatment strategies.

To address this knowledge gap, this paper summarizes data trends compiled from all known literature published globally on the disease and includes a comprehensive review of the outcome of treatment methods employed.

$451k

estimated annual treatment costs for an MVID patient on total parenteral nutrition (TPN)



147%

increase in reported MVID cases from the 5-yr. period 2006 - 2010 to the period 2011- 2015

0

number of accessible, reliable long-term MVID treatment options

Microvillus inclusion disease (MVID)

Microvillus inclusion disease (MVID) is an exceedingly rare intestinal disease presenting early in the neonatal period, with affected infants developing intractable diarrhea within hours, days, or months after birth. The severity of diarrhea in MVID patients is such that patients are unable to absorb fluids, nutrients, or electrolytes; thus malnutrition and dehydration are inevitable and often lethal if the condition is not appropriately treated.

The inherently small population of patients with MVID presents challenges regarding the breadth of scientific and medical knowledge pertaining to the disease. This means that diagnosis can require long-distance travel to visit multiple hospitals and specialists over the course of several months. In areas without medical expertise of the disease, families and doctors of MVID patients often conduct their own research to better understand the disease.

Given the rarity of MVID, most case reports are either single reports or compilations of previous cases. Individual characteristics and data trends related to the disease have not previously been compiled. This paper includes the first comprehensive analysis of all known literature published globally on MVID since the first case report (356 reports total, spanning from 1978 to 2017) - aggregating data related to patient location, gender, disease onset, and outcomes of the various treatment strategies employed.

Additionally, this paper analyzes the mechanism behind attempted treatment strategies demonstrating any degree of positive outcome, concluding that no effective long-term treatment strategies currently exist outside of total parenteral nutrition (TPN) and small bowel transplantation. This indicates a need for the accelerated development of new medicine to improve the quality of life and extend the lifespan of MVID patients.

"This indicates a need for the accelerated development of new medicine to improve the quality of life and extend the lifespan of MVID patients."

What is MVID?

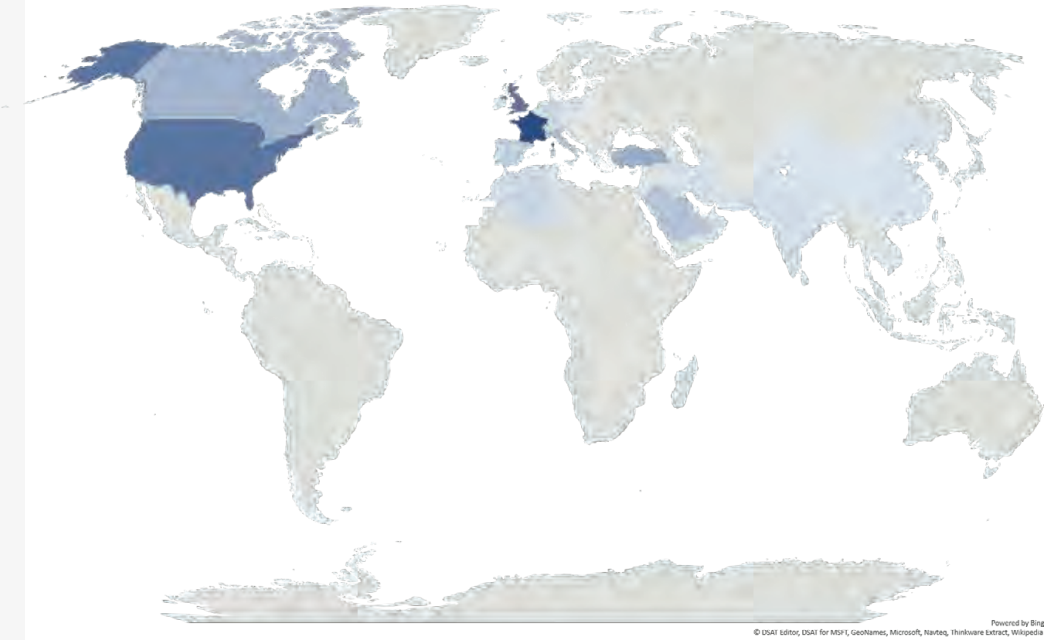
MVID is a rare, hereditary enteropathy presenting in neonates; characterized by life-threatening volumes of watery diarrhea. MVID is an autosomal- recessive congenital disease affecting predominantly intestinal epithelial cells, caused by a mutation in the MYO5 gene that limits the growth and function of these cells.

The intestine of an MVID patient is out of balance. It severely and continuously secretes much more than it absorbs because the genetic defect of MVID impairs proper development of cells and ion channels, which would normally drain or absorb fluid from the gut. Instead, the cells are frozen in an immature state where their main task is to secrete fluids into the intestine. This causes the intestine to overflow, resulting in serious diarrhea. Critical nutrients, water, and electrolytes are lost in the stool; and therefore not absorbed into the body when the infant eats or drinks. Because of this imbalance, an infant with MVID can lose up to one

Figure 1

Global Distribution of MVID Cases

Darker hue indicates a higher number of reported cases.



third of his or her body weight each day.

Diagnosis

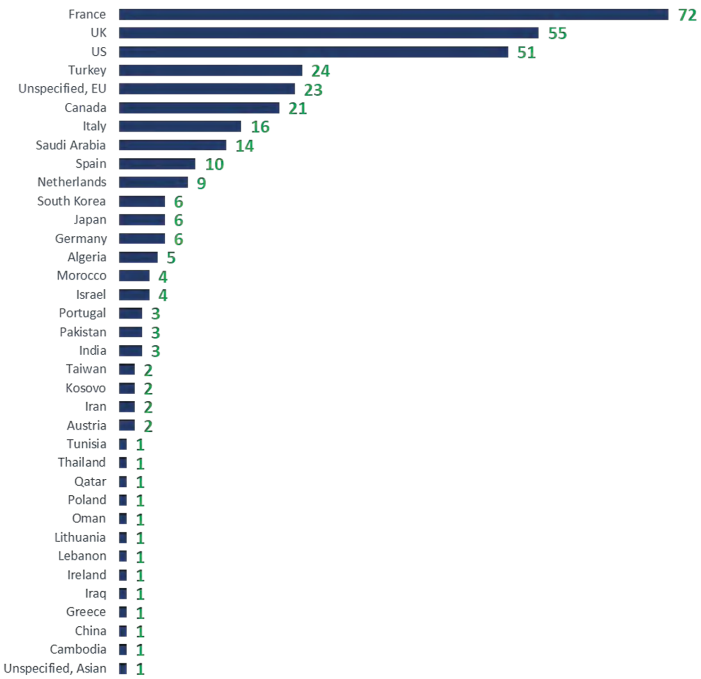
MVID is very difficult to diagnose; the reason for this is two-fold. First, the disease is extremely rare and therefore largely unknown to the pediatric community. Second, confirmation of MVID requires sophisticated diagnostic techniques such as electron microscopy of intestinal biopsies. The combination of the necessary equipment to perform the confirmatory electron microscopy, and the highly-trained personnel to conduct the procedure is not readily available in most hospitals around the world. A simple, effective, and readily-available means to diagnose the disease does not currently exist.

Affected infants typically spend the first months of their lives in the hospital and receive a diagnosis within two to three months. It is common for patients to travel to two or more hospitals seeking diagnosis and an appropriate course of treatment. A well-known and accessible test to diagnose MVID could improve doctors' ability to determine a treatment strategy earlier in these infants' lives – a factor that could make all the difference given the short length of their estimated lifespans.

Geographic Distribution of Reported Patient Population

Figure 2

Distribution of MVID Cases by Country



"A well-known and accessible test to diagnose MVID could improve doctors' ability to determine a treatment strategy earlier in these infants' lives – a factor that could make all the difference given the short length of their estimated lifespans."

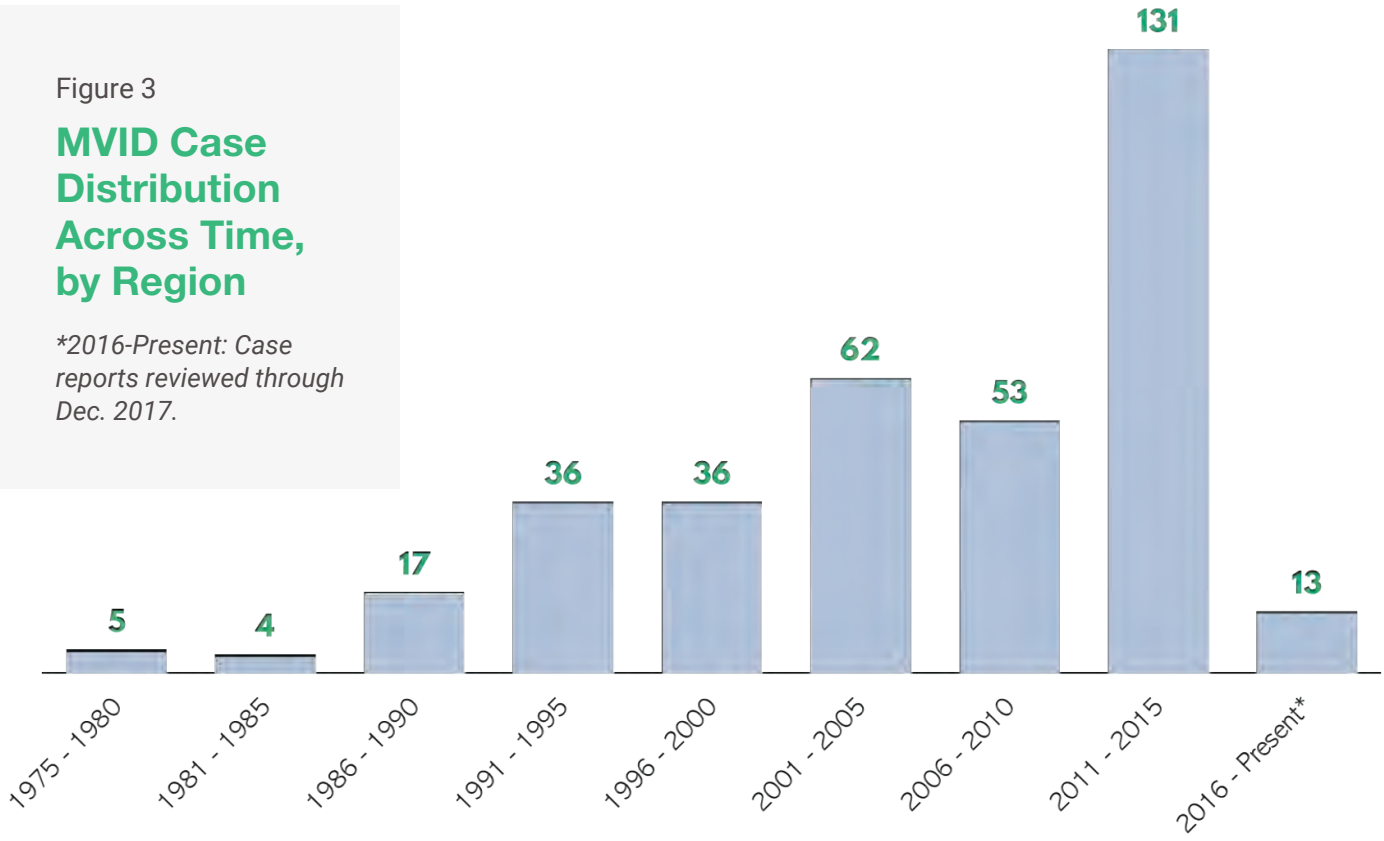
Treatment

The current standard treatment for MVID is total parenteral nutrition (TPN), in which fluids and nutrients are delivered directly to the bloodstream of the patient up to 24-hours a day via IV. Dependence on TPN contributes to a poor quality of life and can result in infection, damage to the veins, and liver failure. Patients who have unmanageable complications due to TPN ultimately seek a small bowel and/or liver transplant; a process which comes with many challenges and risks of its own.

Figure 3

MVID Case Distribution Across Time, by Region

**2016-Present: Case reports reviewed through Dec. 2017.*



Geographic Distribution of Reported Patient Population

356 cases of microvillus inclusion disease were reported globally from 1978 to 2017. Most of these reports originated from Europe and North America – from Europe, 202 individual cases, or 57% of all known cases, were reported in 43 publications.

Of the 202 European cases, France and the United Kingdom represent 72 (20% of all cases worldwide) and 55 (15% worldwide) cases respectively. For North America, 72 individual cases were reported in 28 publications, representing 20% of the worldwide distribution. Of these 72 cases, 51 (14% worldwide) were reported in the United States and 21 (6%) in Canada. Following France, the UK, and the US, the country with the next highest incidence is Turkey, with 24 reported cases (7%). The remaining cases were scattered among 19 countries and one unspecified Asian region. Plotting the clinical case reports on the world map reveals that the highest concentration of countries with reported cases of MVID is in the Western hemisphere.

Case Distribution Across Time

Since the initial classification of the disease, the number of cases reported has increased substantially throughout the years. Relatively few new cases were reported in the ten-year period from 1975 through 1985. However, in the next five-year period (1986-1990) there were over four times as many cases reported at 17 worldwide; over the subsequent five-year period (1991 – 1995), this number more than doubled to 36 cases. Cases remained relatively high from 1991 through 2015, with a notable spike of 147% more cases (over the previous five-year period) from 2011 through 2015.

For the period January 2016 through December 2017, 13 cases were reported at the time of this publication. Given that this period spans two calendar years, rather than the five years represented in all other categories in Figure 3, and factoring in an anticipated gap between disease diagnosis and published case report (i.e., it is not likely that all known cases from 2016– 2017 have been published at the time of this analysis), this number should be excluded

Figure 4

MVID Case Distribution Across Time, by Region

2016-Present: Case reports reviewed through Dec. 2017.

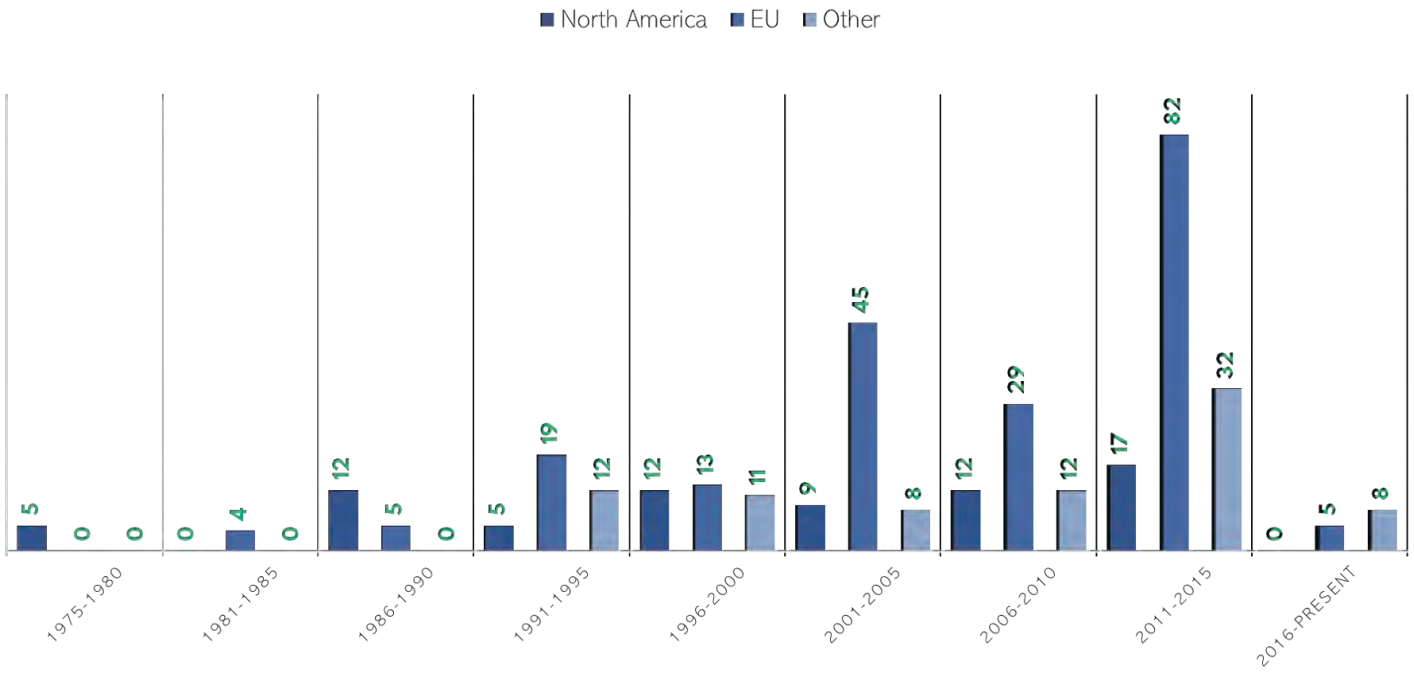


Figure 5

Gender Distribution of MVID Cases

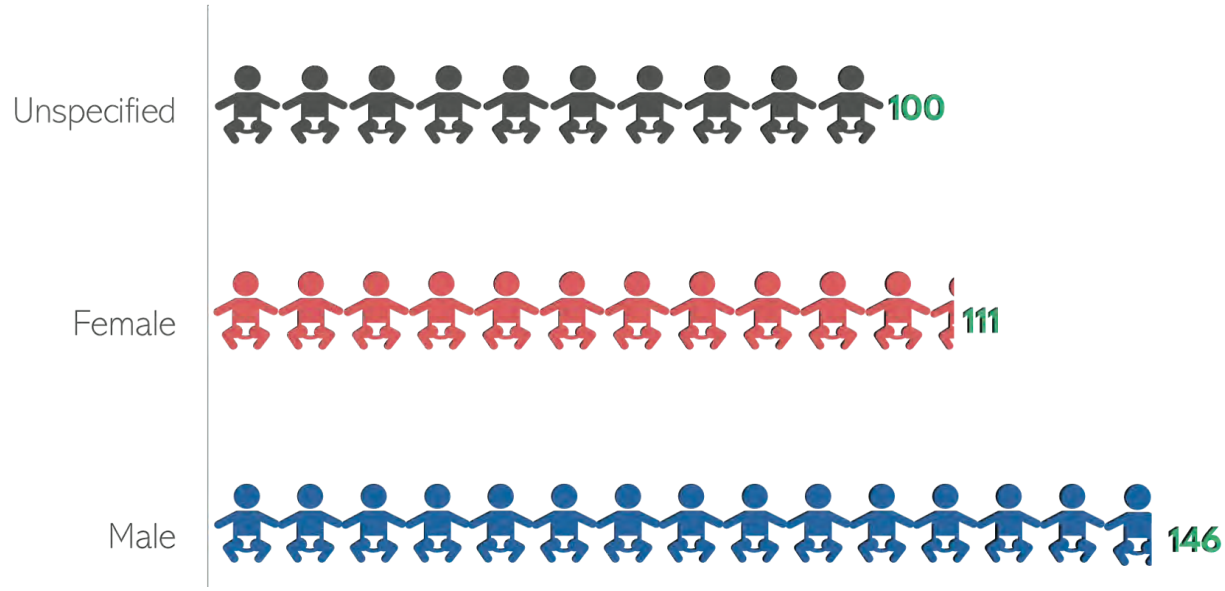
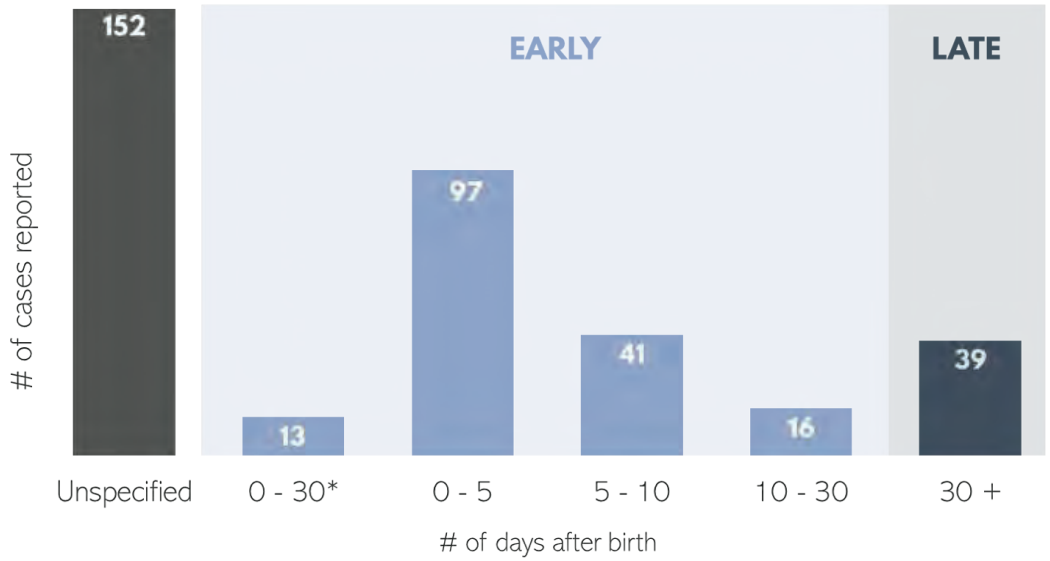


Figure 6

Onset of MVID

*Cases in the "0-30" days category indicate this range was provided, but exact day of onset was not further specified.



from consideration of the overall upward trend in number of cases reported across time.

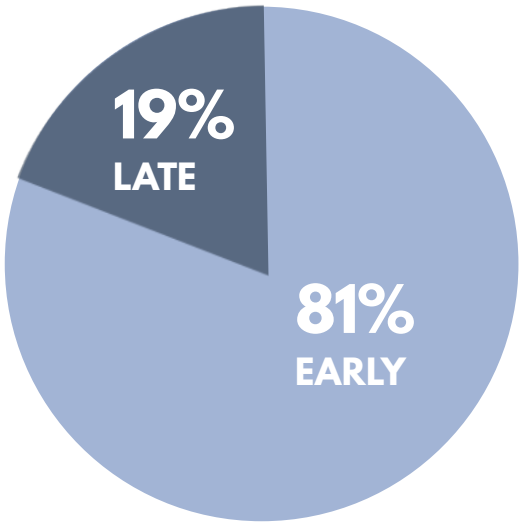
Case Distribution Across Time, by Region

For purposes of this analysis, case reports have been divided into three categories: Europe, North America, and Other, which encompasses the remaining 20 countries/regions with reported cases. This division was made based on the distribution of cases, with Europe representing 57% (202 cases) of all worldwide cases and North America representing 20% (72 cases). The remaining 23% of cases (82 cases) were scattered around the world.

This distribution is likely due in part to patients being transferred to major hospital centers from smaller countries, seeking a diagnosis and appropriate course of care. The absence of an adequate and accessible screening test around the world contributes to this imbalance towards major systems in Europe and North America, and to misdiagnosis of the disease altogether.

Figure 7

Onset of MVID, Unspecified Cases Excluded



Disease Onset

"Early onset" of the disease is defined by the National Institutes of Health (NIH) as MVID symptoms presenting within the first 30 days of an affected infant's life. All cases in which symptoms present at any point after these first 30 days are defined as "late onset." Of the 356 cases reviewed, 152 reports did not specify disease onset.

Of the 206 cases with a reported date of onset, 81% were found to be early, and 19% late. Further, it was found that in almost half (47%) of these cases, onset occurred within the first 5 days after the affected infant was born; in 20% of cases, onset occurred between 5 and 10 days; and in 8% of cases, onset occurred between 10 and 30 days. An additional 6% of cases were reported as "early onset," but the exact day of first appearance was not further specified.

Cost of Treatment

Treatment of MVID is extremely expensive – in 2008, one MVID patient's family reported racking up medical bills totaling $1M USD within the first 8 months of their child's life. Raper et al. reported in 2002 that the average annual cost for "multi-compartment, 'big bag' total parenteral nutrition in an ICU" was around $182,000 (~ $255,000 when adjusted for inflation, according to the U.S. Bureau of Labor Statistics); with TPN patients encountering around $140,000 (~ $196,000, adjusted for inflation) in additional expenses associated with hospitalization. This equates to a total of $322,000 each year (~ $451,000, adjusted for inflation).

The estimated price of intestinal/small- bowel transplantation, considered to be the most effective long-term method of treatment for MVID, was reported by Bentley et al. in 2017 to be around $1.6

Cost of Treatment

$451,000

Estimated total to care for MVID patient via TPN, per year

$1.6M

Estimated price of small bowel transplantation

million, with an additional annual expense of $40,000 for ongoing immunosuppression.

The significant costs associated with MVID are shared both by families of MVID patients and the healthcare financial support systems of their given countries.

Treatment Methods

Since the identification of MVID in 1978, most reported cases were treated with TPN and small bowel transplantation; some have included trials of enteral (oral) nutrition, which has been found to aggravate the condition further. Anti-diarrheal pharmaceuticals have been attempted in many cases as well, often with little to no observed therapeutic response. While there is currently no cure for MVID, there have been four isolated cases of spontaneous recovery from the illness (Perry et al., 2014).

Total Parenteral Nutrition (TPN)

The most common method for managing MVID is total parenteral nutrition (TPN), in which fluids and nutrients are delivered directly to the bloodstream of the patient via IV, and no nutrition is ingested. Due to the severity of diarrhea experienced by MVID patients, TPN is often administered continuously for 20 to 24 hours a day. Dependence on TPN contributes to poor quality of life; and can result in infection, damage to the veins, and liver failure.

Small Bowel Transplantation

Patients who have unmanageable complications due to TPN will ultimately seek a small bowel and/or liver transplantation, a process which comes with many challenges and risks of its own. Small-bowel transplantation is considered at present to be the most effective method of treatment for MVID. Halac et al. conducted a study from 1995 to 2009, analyzing 24 MVID patients, 13 of which underwent small-bowel transplantation. Of the patients studied, it was found that over this 14-year period, the survival rate without small-bowel transplantation was 63%, and the survival rate with transplantation was 77%; the subsequent term of life for patients that underwent transplantation ranged from 0.4 to 14 years (Halac et al., 2011). In many cases, small-bowel transplantation can be unattainable given the high costs associated with the procedure and/or the difficulty of locating an appropriate donor.

Treatment Methods

Anti-diarrheal Pharmaceuticals

Treatment with anti-diarrheal pharmaceuticals has been attempted in many cases, often with no observed therapeutic response. In rare cases, patients have experienced a somewhat positive response to anti-diarrheals, showing reduced stool volume outputs.

A summary of all known anti-diarrheal treatments attempted for MVID, and the reported outcome for each is provided in Table 1.

[table]

As indicated in Table 1, some of the anti-diarrheals listed led to reduced stool output to varying extents and, in the case of EGF/Urogastrone, increased microvillus population. However, it is important to note that in all cases, any positive effect observed was minimal or transient, and no treatment attempted was successful to the extent that the need for TPN was eliminated. A summary of anti-diarrheal treatments with reported positive outcomes is included in Table 2.

[table]

Reported Lifespan and Cause of Death

From the data reviewed, it is not possible to definitively analyze MVID survival rate or lifespan as cases have been reviewed from as early as 1978; and up-to-date information on patient status following publication is not available. Of the 356 cases reviewed, 101 patients were reported to be deceased at the time of case report publication, and lifespan was not reported for 39 of the 101 patients. The reported lifespan of the deceased is summarized in Figure 8.

Table 1

Attempted Anti-diarrheal Treatments and Reported Outcomes

Antidiarrheal	Outcome	Halted TPN?	Reference
ACTH	No response	No	Phillips et al., 1985
	No response	No	Davidson et al., 1978; Bell et al., 1991; Rhoads et al., 1991; Phillips and Schmitz, 1992; Beck et al., 2001; Ukarapol et al., 2001
Cholestyramine	Variable efficiency	No	Girard et al., 2014
	Reduced stool output from 150g/kg/day to 50g/kg/day	No	Beck et al., 1997
Chlorpromazine	No response	No	Phillips and Schmitz, 1992
Cisapride	No response	No	Phillips and Schmitz, 1992
Cimetidine	No response	No	Phillips and Schmitz, 1992
Clonidine	Negative response	No	Rhoads et al., 1991
EGF / Urogastrone	No response	No	Walker-Smith et al., 1985; Drumm et al., 1988; Cutz et al., 1989; Phillips and Schmitz, 1992
	Increased microvillus population, but no effect on villus atrophy	No	Beck et al., 1997
Glucocorticoids (hydrocortisone, prednisolone)	No response	No	Davidson et al., 1978; Phillips et al., 1985; Drumm et al., 1988; Cutz et al., 1989; Bell et al., 1991; Phillips and Schmitz, 1992; Herzog et al., 1996
Loperamide	No response	No	Phillips et al., 1985; Bell et al., 1991; Tran et al., 2017
	Partial reduction in stool output	No	Phillips and Schmitz, 1992; Pohl et al., 1999
Octreotide	No response	No	Rhoads et al., 1991; Herzog et al., 1997; Beck et al., 1997; Ukarapol et al., 2001; Mendes et al., 2014
Oral disodium chromoglycate	No response	No	Phillips et al., 1985
Pentagastrin	No response	No	Davidson et al., 1978; Cutz et al., 1989
Probiotics	No response	No	Ukarapol et al., 2001
Ranitidine	No response	No	Burgis et al., 2013
Racecadotril	Transient reduction in stool output and frequency. The effect was replicated to a lesser degree after the treatment paused.	No	Tran et al., 2017
Somatostatin	No response	No	Cutz et al., 1989; Bell et al., 1991; Schoffield et al., 1992; Pohl et al., 1999
	Reduction or minor reduction in stool output	No	Phillips and Schmitz, 1992 (2 cases); Groisman et al., 1993

Table 2

Attempted Anti-diarrheal Pharmaceuticals with Reported Positive Outcomes

Antidiarrheal	Outcome	Halted TPN?	Reference
	Variable efficiency	No	Girard et al., 2014
Cholestyramine	Reduced stool output from 150g/kg/day to 50g/kg/day	No	Beck et al., 1997
EGF / Urogastrone	Increased microvillus population, but no effect on villus atrophy	No	Beck et al., 1997
Loperamide	Partial reduction in stool output	No	Phillips and Schmitz, 1992; Pohl et al., 1999
Racecadotril	Transient reduction in stool output and frequency. The effect was replicated to a lesser degree after the treatment paused.	No	Tran et al., 2017
Somatostatin	Reduction or minor reduction in stool output	No	Phillips and Schmitz, 1992 (2 cases); Groisman et al., 1993

Of the 101 reported cases in which the patient was deceased at the time of publication, only 44 specified a cause of death. The limited available data implies that the leading primary cause of death for MVID patients is sepsis (61% of reported cases) followed by liver failure (14%).

Conclusion

In areas without medical expertise of microvillus inclusion disease, families and doctors of patients will often seek research to understand the disease better. Given MVID's rarity, it can be difficult for doctors, researchers, and parents confronted with the disease to locate necessary data; presenting challenges with research, diagnosis, and development of treatment strategies. This resource was compiled to provide the first comprehensive analysis of existing literature on MVID; analyzing 95 articles containing 356 original case reports from 1978 to 2017. It should be noted that any statements made within this paper have been deduced based on the known clinical case reports publicly available online, and that single cases recorded in multiple reports (i.e., cohort studies) cannot be identified or accounted for given the confidentiality of clinical cases.

Since MVID was established as a disease in 1978, global reports have grown substantially, with Europe experiencing the highest level of growth compared to other regions of the world. This may be due in part to a general increase in awareness of the relatively new rare disease.

Additionally, patients are often drawn to major centers from smaller regions, as diagnosis can require long-distance travel to visit multiple hospitals and specialists. A well-known and accessible test to diagnose MVID could improve doctors' ability to both identify the disease and determine a treatment strategy (or appropriate center for treatment) earlier in affected infants' lives, despite location or specialization.

Other data compiled in this analysis indicated that slightly over half of affected patients are male, and that MVID typically presents within the first 30 days of an infant's life. While it is not possible to definitively analyze survival rate or lifespan from the information collected, data on those reported deceased at the time of case publication implied that most patients pass away before reaching two years of age.

The treatment methods currently considered to be the most effective for the management of MVID are total parenteral nutrition (TPN) and small bowel transplantation. It is generally understood that the methods are accompanied by health issues and poor quality of life and this analysis further confirmed the serious com-

Figure 8

Lifespan of MVID patients reported deceased

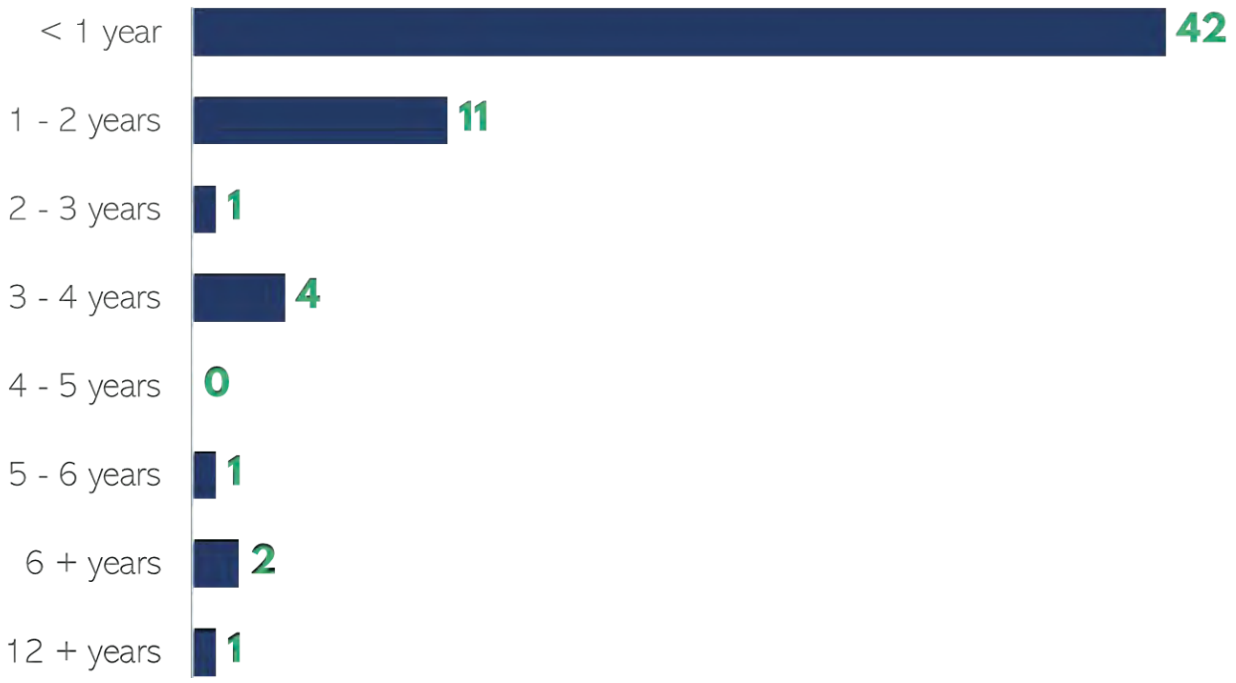
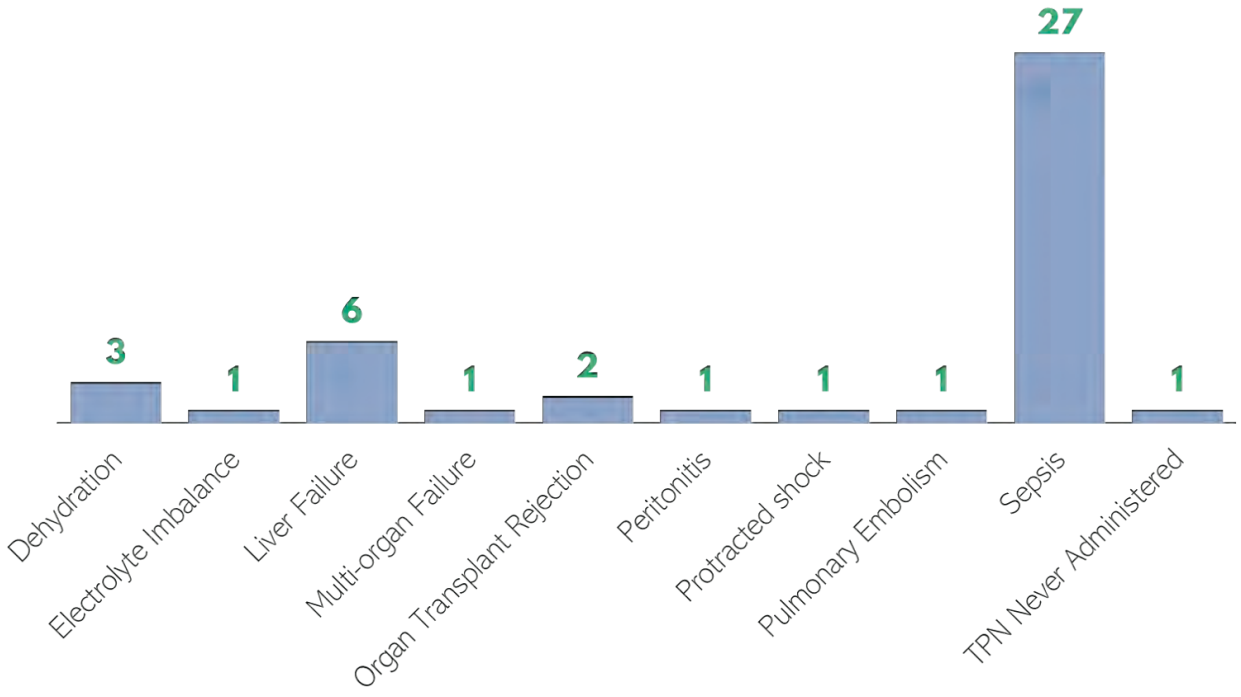


Figure 9

Reported primary cause of death



plications of these treatment strategies by indicating that the primary known causes of death in MVID patients are infection, liver failure, and transplant rejection – all outcomes associated with the preferred treatment options available.

This paper also analyzed attempted alternative (anti-diarrheal) treatment strategies. Of all cases reviewed, a handful of alternative methods led to a reduction in stool output; however, any positive outcome was minimal or transient. No alternative methods attempted have resulted in the elimination of TPN-dependence for any patient. This - coupled with the poor prognosis associated with the standard treatment methods - further underscores the need for the accelerated development of new medicine to improve the quality of life and extend the lifespan of MVID patients.

The Future for MVID Patients

The first step towards a brighter future for MVID patients would be the development of an effective, easily available, and easily- administered diagnostic test. This would greatly improve the ability for doctors to recognize the disease early, and therefore begin work to either determine the best course of treatment for the patient or to determine the best facility to provide specialized treatment. The current diagnostic limitations are likely leading to under-diagnosis and misdiagnosis, and given the demanding treatment needs of this disease, there is no time to waste when it comes to caring for MVID patients.

As far as treatment is concerned, the development of new medicine is required for long-term management of MVID. The current methods – total parenteral nutrition and small bowel transplantation – have proven to be riddled with potentially lethal health complications and require strict, difficult, and expensive maintenance.

Gene therapy could be a distant possibility, but it is not currently under consideration for this disease. Although none of the alternative anti-diarrheal remedies that have been attempted for treatment of MVID have been effective to the extent that the need for TPN was eliminated, doctors and researchers are taking positive steps towards an effective treatment by targeting different mechanisms of action of the disease. A future possibility may be a treatment focused on “turning on” the pathways in those intestinal cells which are not impacted by the genetic mutation, allowing the MVID intestine to function as a healthy intestine would. Regardless of the exact mechanism of treatment, children affected by MVID are desperately in need of new, alternative options that will improve their quality of life and extend their life expectancy.

Acknowledgments

The authors acknowledge Dr. Richard Lutes, Zachary Robbins, and Alessandro Woodbridge for their input and assistance with the preparation of this document.

Our hearts go out to all families impacted by this difficult disease. The strength exhibited by both the families of children affected by MVID, and by the patients themselves, is commendable and beyond compare.

A list of hospitals, diagnostic centers, and non-profits that support patients and their families can be found at mvid.vanessaresearch.com/patient-resources.

Appendix A:

Mechanism of action for anti-diarrheal pharmaceuticals used in attempted treatment of MVID, with the appearance of positive outcome

Cholestyramine is a resin that prevents re-absorption of bile by binding it in the gastrointestinal tract. It is an ion exchange resin, meaning it can exchange its chloride anions with anionic bile acids in the gastrointestinal tract. It has the functional center and a quaternary ammonium group (which is attached to an inert styrene-divinylbenzene copolymer). Cholestyramine resin absorbs the bile acids in the intestine forming an insoluble complex which is excreted in the feces (Drugbank, 2018).

EGF, known as Urogastrone, is a protein with size 6-kDa (Harris RC, 2003) and consists of 53 amino acid residues and three intramolecular disulfide bonds (Carpenter G, 1990). It stimulates cell proliferation, growth and differentiation by binding to its specific binding site, receptor, EGFR and activating GTP/MAPK cascade. Human EGF exerts trophic effects on the internal intestine surface and may be involved in maintaining normal intestinal structure and function. Consequently, it is important in cases in which nutrients are administered parenterally, as parenteral nutrition can result in intestinal hypoplasia and hypofunction.

Loperamide acts as the μ-opioid receptor agonist/calcium channel antagonist along the small and large intestine to decrease circular and longitudinal muscle activity through the neural mechanism in the peripheral nervous system (Drugbank, 2018). Loperamide exerts its anti-diarrheal action by causing an increase in the time fecal matter stays in the intestine, allowing more water to be reabsorbed. (US Government, 1993).

Racecadotril is a peripherally acting enkephalinase inhibitor (Matheson, 2000). Unlike other opioid medications which treat diarrhea by reducing intestinal motility, racecadotril reduces the secretion of water and electrolytes into the intestine (Matheson, 2000), resulting in an anti-secretory effect. Racecadotril’s active metabolite, thiorphan, inhibits the enzyme neutral endopeptidase (NEP) and increases exposure of cells to NEP substrates such as enkephalins and atrial natriuretic peptide (ANP). Endogenous enkephalines are active on both μ- and δ- opioid receptors (Huighebaert et al., 2003). NEP inhibition will also increase exposure of cells to endogenous neuropeptide Y and, possibly, peptide YY, both of which have strong anti-secretory effects in the gut (Playford and Cox, 1996).

Somatostatin is a peptide hormone that is considered to be an anti-secretory. It acts on neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors. Somatostatin, also known as a growth hormone–inhibiting hormone (GHIH), regulates the endocrine system and inhibits the release of secondary hormones. It acts as a powerful inhibitor of intestinal Cl− secretion and inhibits one kind of basolateral K+ channels in human intestinal crypt cells via a G protein- dependent mechanism, which may result in a loss of the Ca2+sensitivity caused by K+ channels. (Sandle, 1999).

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