Management and Survival of Meconium Ileus

A 30-year Review

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Cystic fibrosis patients born with meconium ileus (MI) have had an improved outcome over the last three decades. The authors reviewed the impact of surgical management and long-term nutritional care on the survival of patients with MI. Of the 59 cases of MI seen from 1959 to 1989, 48 cases were managed operatively using either the Bishop-Koop ileostomy (BK), the Mikulicz ileostomy, primary resection and anastomosis (RA), or ileotomy. Six-month survival of MI has improved from 37% to 100%. Nonoperative cases (n = 11) had 100% long-term survival. The RA survivors required less late operative intervention (20%) as compared with other surgical patients (81%). A comparison of serial growth percentiles of CF patients with MI with those of their non-MI CF peers showed similar long-term decreases. These data confirm: (1) There is an improved survival for MI independent of the surgical procedure; (2) The BK ileostomy is an effective and time-tested MI treatment; (3) Primary resection and anastomosis in selected cases may have a lower surgical morbidity rate; and (4) Meconium ileus does not adversely affect the long-term nutritional outcome of CF patients.

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MECONIUM ILEUS (MI) IS one of the most common causes of intestinal obstruction in the newborn, and often this obstruction is due to obturation by intraluminal, abnormally viscid meconium.[1,2] Meconium ileus occurs in 10% to 20% of infants with cystic fibrosis (CF) and is frequently the first manifestation of their disease.[3] Cystic fibrosis is a disorder of the exocrine glands, characterized by chronic lung disease and malnutrition secondary to pancreatic insufficiency. It occurs in approximately 1 in 2000 live births in caucasian and less frequently in black and Oriental populations.[4] Cystic fibrosis is an autosomal recessive trait and is the most common lethal gene in the caucasian population. The gene and its most common mutation were recently identified.[5,6] The MI relationship with pancreatic fibrosis has been recognized since 1905, when it was first reported by Landsteiner.[7]

The purpose of this investigation was to review the cases of MI in newborns with CF since 1959 at the Children's Hospital of Philadelphia. The review was used to document the effect of nonoperative and surgical approaches in MI, to examine the cause of 6-month mortality rates, and to compare the individual surgical groups' survival. Additionally, an assessment of the MI patients' long-term growth and nutrition was compared with those of their non-MI CF peers.

Methods

Study Population

A retrospective analysis of newborn MI cases was performed. Of the 81 newborns found with a diagnosis of meconium obstruction diagnosis, 59 were confirmed to have CF with MI during the years 1959 to 1989. Surgical patients (n = 48) included only those cases operated on at our institution.

The diagnosis of CF was confirmed by two positive sweat tests using quantitative pilocarpine iontophoresis (sodium chloride > 50 mEq/L).[8] In addition, stool trypsin determination (trypsin < 80 μg/g stool) and operative findings were used to support the diagnosis of MI and CF.[9] Characteristic operative findings included a markedly dilated loop of small bowel with the immediate distal ileum beyond the massive loop firmly packed with a viscid, puttylike meconium quite adherent to the mucosal lining.[10] The distal ileum and the ascending colon appeared beaded with a colon smaller in diameter than expected.

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Intestinal gland dilatation also was seen on histologic examination.[11] In the last decade, diagnosis of CF was also predicted by restriction fragment length polymorphisms (RFLP) analysis on prenatal amniotic fluid.[6]

Nonoperative treatment

Eleven patients with MI, who were thought to have simple cases with no other intestinal complications such as volvulus or atresia, were treated nonoperatively by nasogastric decompression, intravenous hydration, and antibiotic therapy. Attempts to evacuate obstructing meconium by contrast enemas were undertaken as originally described by Noblett.[12] Gastrografin, a hyperosmolar solution (aqueous saline methylglucaine diatrizoate) was instilled per rectum, in the radiology suite under fluoroscopic guidance.[13]

Operative Treatment

Surgical intervention was required in 48 MI patients. The Gastrografin enema failed to relieve the obstruction in 16 simple cases. Complicated cases (n = 34) all required surgery and included those with volvulus, perforation, meconium peritonitis, intestinal atresia, gangrene, or meconium cyst.[10] Therapeutic Gastrografin enema was reserved for simple cases of MI.

Operative methods included one of several ileostomy decompressions (Fig. 1A–C) or primary resection and anastomosis (RA) (*e.g.*, Swenson's technique, Fig. 1D).[14–16] Techniques of decompression included: (1) ileotomy with placement of a tube catheter for irrigation with acetyl cysteine, saline, or pancreatic enzymes (Fig. 1A); (2) construction of a double-barreled Mikulicz ileostomy with resection of the large dilated loop (Fig. 1B); or (3) the Bishop–Koop procedure (BK), a Roux-en-Y

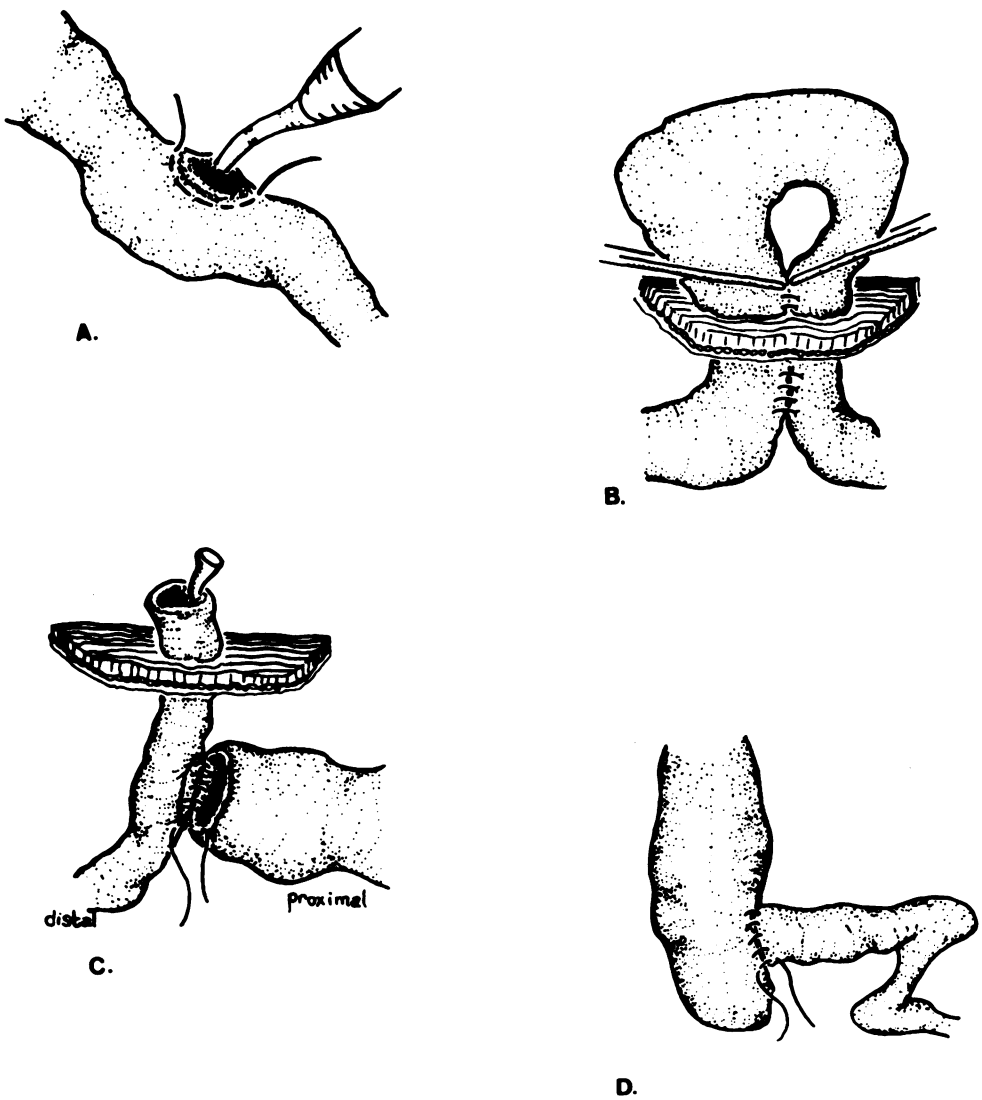

FIG. 1. Various operative approaches for MI. (A) Ileotomy with irrigation. (B) Mikulicz ileostomy. (C) Bishop–Koop ileostomy. (D) primary anastomosis.

anastomosis and ileostomy, with removal of the maximally distended proximal segment and the establishment of a "safety valve" (Fig. 1C).

If bacterial contamination was suspected in complicated cases, double-barreled intestinal exteriorization was used. The BK repair was used in both simple and complicated MI cases, with the RA procedures reserved for nonperforated cases. Ileotomy with irrigation was generally reserved for simple cases. Volvulus, atresias, perforated, or gangrenous intestine was resected, and viable distal intestine was subsequently cleared of meconium plugs with either a mucolytic agent or Gastrografin. In a number of instances, distal obstructing plugs were removed at the time of operation.

Analysis

Statistical significance was determined using chi square analysis and cumulative Mantel–Cox survival curves.[17] Recent follow-up (within the past year) was available on 52 of the 59 patients.

Nutritional Assessment

Data on birth weight and recent heights and weights were collected from MI patients (n = 19) and non-MI CF patients (n = 19) from the years 1972 to 1989. Four of the MI patients were treated nonoperatively; the other 15 underwent surgery. Each MI patient was matched by sex, date of birth (within 12 months of the date of birth), and birthweight to a non-MI CF peer. Their growth data were standardized using the normal growth curves from the National Center for Health Statistics (NCHS) percentiles.[18] A t test comparing MI and non-MI CF groups by height percentile (most recent follow-up) and changes in weight percentile (between birth and recent follow-up) was performed to assess long-term nutritional outcome. Percentile ranges were graded from 1 through 8, corresponding to ranges of: <5%, 5% to 10%, 10% to 25%, 25% to 50%, 50% to 75%, 75% to 90%, 90% to 95%, and >95%, respectively. The t test was performed on the grades corresponding to the children's percentiles for weight and height.

Results

Of the 59 children studied, there was parity with regard to gender (29 male, 30 female). Gestational age of the newborns averaged 39 weeks ± 2.2 (n = 49), ranging from 31 to 44 weeks. The racial ratio was 58:1, caucasian to black, respectively. Birth weight averaged 2.86 kg ± 0.96 (n = 54), with a range of 1.85 to 4.2 kg.

All patients had clinical findings of intestinal obstruction with radiologic or sonographic confirmation. Abdominal sonography was used in three patients, assisting in the prenatal diagnosis of MI by demonstrating dilated loops and small bowel obstruction in the fetus. One MI patient was identified by chromosomal analysis of amniotic fluid after a sibling was diagnosed with CF.

Results of Management

Initial management was either nonoperative (n = 11) or surgical (n = 48). There was one perforation during a nonoperative decompressive enema that required a terminal ileostomy. Surgical procedures included ileostomy (n = 4), resection with primary anastomosis (n = 6), exteriorization and resection with double-barreled Mikulicz ileostomy (n = 4), and Bishop–Koop ileostomy (n = 34).

Complicated cases at initial diagnosis (n = 32) included those with volvulus (n = 21), meconium peritonitis (n = 14), gangrene (n = 3), perforation (n = 8), intestinal atresia (n = 8), or meconium cyst (n = 1). Some cases had multiple complications. Six of the perforations were found in the small bowel, and two others in the colon.

Long-term mortality rates were similar between sexes, 31% (n = 29) of males surviving overall, and 30% (n = 30) of females.

Nonoperative patients contributed to the improvement of overall MI survival before 1979 (n = 8) (Fig. 2); however, in the 1980s both nonoperative (n = 3) and surgical patients (n = 20) had 100% survival ($p < 0.0001$).

Significant improvement was seen after the 1960s, when the surgical 6-month survival was 33% (n = 15) (Table 1). The total 6-month operative survival before 1979 was 60% (n = 28), improving to 100% (n = 20) from 1979 to 1989.

Of the children who died before 6 months (10 from the 1960s, and one from the 1970s), three had postoperative intraperitoneal leakage, four died of pulmonary sepsis and bronchopneumonia (including *Pseudomonas, Klebsiella,*

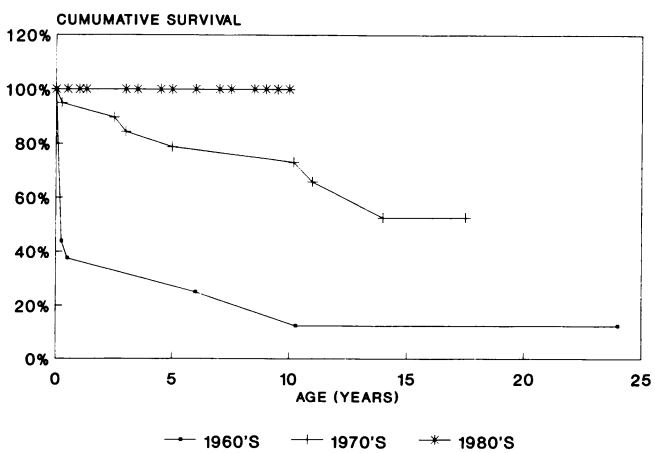

FIG. 2. MI long-term survival by decade. MI has shown improved survival when the 1960s, 1970s, and 1980s survival curves are compared. Generalized Savage (Mantel–Cox) test $p < 0.0001$.

TABLE 1. *Six-Month Survival: Comparison of Operative Procedures and Complicated* Versus *Simple Cases*

Operative Procedure	Complicated (%)	Simple (%)	Total (%)
BK 1960s	1/4 (25)	3/6 (50)	4/10 (40)*
Non-BK 1960s	0/3 (0)	1/2 (50)	1/5 (20)*
Surgical 1960s	1/7 (14)	4/8 (50)	5/15 (33)
BK total	17/20 (84)	10/14 (71)	27/34 (79)*
Non-BK total	9/12 (77)	1/2 (50)	10/14 (71)*
Surgical total	26/32 (81)†	11/16 (69)†	37/48 (77)

* Comparison of survival rates for BK and non-BK procedures in the 1960s and the total 30-year period. $p > 0.1$ NS by chi square with Yates correction.

† Comparison of survival for all complicated and simple cases over the 30-year period. $p > 0.1$ NS.

and *Enterobacter*), three had septicemia (including *Pseudomonas, Escherichia coli,* and *Bacteroides*), and one child with erythroblastosis fetalis had a fatal intra-abdominal hemorrhage. The postoperative intraperitoneal leakages associated with death were: (1) at the site of a BK anastomosis; (2) where an intraluminal rubber irrigation catheter had inadvertently perforated the small intestine in a BK patient; and (3) at a gastrostomy site in a BK patient. The one other leakage with associated complications was an ileotomy closure that disrupted and required reoperation.

When comparing both 1960s and overall 6-month operative survival for the BK cases and all other operative repairs (Non-BK), no significant difference was demonstrated between groups (Table 1). Comparison of these groups for the 1970s did not yield significant information because of there being only one non-BK surgery, and for the 1980s all surgical cases survived despite the type of repair. Long-term survival as tested by the Mantel-Cox survival model (Fig. 3) shows that 6-year survival of BK patients (62%) is similar to that of non-BK surgical patients (72%). The survival is significantly better in the nonoperatively treated group than in either surgical group (*e.g.*, Fig. 3 shows survival at 2 years to be 80% and 72.5% for BK and non-BK groups, respectively, and 100% for nonoperatively managed patients, $p = 0.0132$). However, all deaths in patients older than 6 months ($n = 8$) were related to underlying CF disease and not to surgical complications; all these children had BKs and died with either cardiopulmonary failure ($n = 2$) or with pneumonia ($n = 6$).

Simple operative cases ($n = 16$) had comparable 6-month survival despite different operative approaches (Table 1), particularly when comparing surgical non-BK with BK procedures, 50% and 71.4%, respectively. Complicated and simple cases had similar 6-month and long-term survival, regardless of surgical procedure (Table 1 and Fig. 3). Complicated surgical cases also had comparable survival rates (BK 84%, $n = 20$; RA 83%, $n = 6$, Mikulicz 75%, $n = 4$). Ten-year survival was 72% for both simple and complicated cases (Generalized Savage [Mantel–Cox] $p = 0.81$).

The survival and morbidity rates of groups requiring stomal closure also was examined. Of the 27 BK patients that survived, six had their ileostomy stoma simply ligated with no further intervention, and 21 patients (78%) required eventual extraperitoneal operative closures of the stoma. Of the 10 children who survived non-BK surgical procedures, six required reoperation. Overall the rate of reoperation was not significantly different between surviving BK and non-BK groups (chi square 1.16, $p > 0.1$). Of the RA patients, all were complicated cases ($n = 6$), and five survived. One patient developed a late small bowel obstruction at 10 months requiring an exploratory laparotomy, lysis of adhesions, and an enteroenterostomy. The RA subset of long-term survivors required less reoperative procedures than all other surgically treated patients (81%, $n = 32$, chi square 8.22, $p = 0.02$). Of the four patients having ileotomy, two survived and both required reoperation. Of the four cases treated by Mikulicz ileostomy, three survived and all had staged formal closures. One nonoperative patient required laparotomy and reduction of volvulus at 6 months because of an omphalomesenteric band as a late complication.

Results of Nutritional Assessment

The long-term nutritional assessment of MI ($n = 19$) and non-MI CF patients ($n = 19$) were paired and compared for weight and height. Of the 19 MI patients studied, 15 were managed surgically. Using weight and height changes, the nutritional status of MI patients was found to be similar to that of non-MI CF patients in long-term follow-up. Serial change between birth and recent follow-

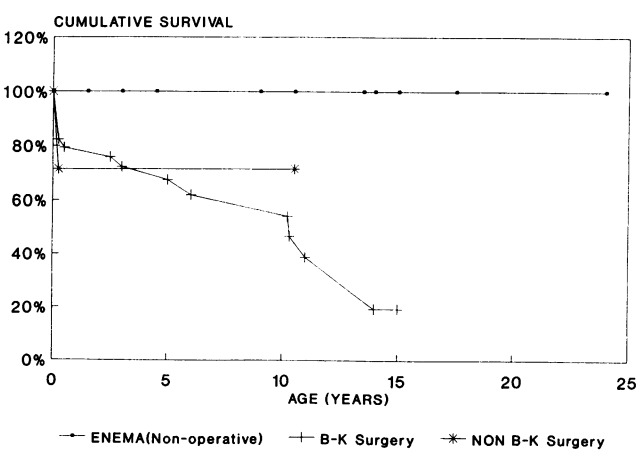

FIG. 3. Treatment and survival of MI: nonoperative *vs.* operative methods. Survival in the period after operation is similar between BK and non-BK surgery. Enema patients have 100% short- and long-term survival. Generalized Savage (Mantel–Cox) test $p = 0.0132$.

up weights demonstrated that both MI and non-MI CF children similarly decreased from an average 50% birthweight percentile to a 10% and 25% age–weight percentile, respectively (t test p = 0.23). Each group had height grades that were similar, spanning the 5% to 25% percentile ranges.

Discussion

An improved outcome in children with MI has been recently demonstrated as compared with the high early mortality rates (ranging from 65% to 79%) as reported since the 1940s by Hiatt and Wilson, Gross and Dey.[15,19,20] Since 1950, major contributions to improved survival include use of the Mikulicz enterostomy (1953),[15] the BK ileostomy (1957),[16] Noblett's description of nonoperative decompression (1969),[12] and Swenson's one-stage resection and primary anastomosis (1969).[14] Application of these techniques has been successful, as that reported by Caniano and Beaver,[21] with a 100% early survival (10 months), and by Rescorla et al.,[22] with 1-year survival rates of 92% for uncomplicated and 85% for complicated MI. Advances in surgical and perioperative management have contributed to current improved 6-month survival of MI patients, especially as seen in the 1980s, with 100% survival.

Several factors have contributed to better management of MI. Improvements in the maintenance of a positive nitrogen balance by the use of parenteral nutrition, particularly for those with long resections or an extended ileus, have had a positive effect on survival.[21,23,24] The combination of nutrient availability and bowel rest appears to promote healing of the anastomoses and closure of fistulae in some cases.[25] Meconium ileus complications such as volvulus and atresias are well known, and their early recognition and advances in their treatment[26,27] may have played a role in recent improved survival compared with that of the 1960s. In recent series, improved complicated survival rates have been consistent with our data; complicated and simple survival rates were 81% and 69%, respectively. Rescorla[22] also reported similar survival rates between complicated and simple cases, and Mabogunje et al.[28] report a drop in complicated mortality rate from 70% before 1962 to 7% between 1963 and 1980.

The children treated by BK ileostomy have shown improved survival rates[2,29] since the method was first described by Bishop and Koop in 1957.[16] A similar improvement in both early and late survival has been seen with other operative procedures. Further surgical intervention was required in surviving BK (77%) and all non-BK surgical cases (60%), with a significantly lower percentage in the RA subset of patients (16%, n = 6). This supports the low morbidity rates reported for RA from other institutions.[28,30] There was only one complication associated with intraperitoneal anastomotic leakage in a BK case in this series. Ileotomy with irrigation was not as successful as that reported by others[31,32] and may be related to the paucity of patients in that subset (n = 4). Our experience suggests that the double-barreled Mikulicz technique is a good alternative for complicated MI.[14,21] The Gastrografin enema decompression method continues to produce exceptional results in selected patient populations.[22,33]

Cystic fibrosis's early mortality rate has been linked to the high morbidity and poor survival rates of MI patients.[34] It has been stated that an MI patient passes a 6-month critical time when he or she has the same prognosis as a non-MI CF patient.[35] An examination of the causes of early death demonstrates that aggressive management of bacterial sepsis and bronchopneumonia with more effective antibiotics has decreased the 6-month mortality rate during the last 30 years. Mortality rates for MI patients related to *Pseudomonas,* coliforms, and other causes of sepsis and bronchopneumonia have been documented by other authors.[2,21,28] Aggressive use of antibiotics, especially aminoglycosides and semisynthetic penicillins, is associated with improved survival in older CF patients, particularly those requiring *Pseudomonas* and gram-negative antimicrobials.[3,36] These organisms were responsible for 6-month and long-term mortality rates before 1979 in our series.

Long-term CF survival has steadily increased over the last several decades, with the approximate median age of survival now being 20 years of age.[3] This has been attributed to development of regionally located CF centers[37,38] that provide education and medical support for all CF patients. Consequently, MI patients have benefited from good chronic pulmonary care as well, resulting in better survival. Pulmonary complications are still responsible for many deaths, however, and remain inevitable in 98% of cases.[3] The early deaths in the 1960s may have been avoided in an era where antibiotics, mucolytics, bronchodilators, steroids, and chronic aggressive chest physiotherapy are routine. There is promise that further improvement in survival may result from specific therapy after description of the CF gene and ultimately the function of the gene product, or immunologic intervention.

Emphasis on earlier diagnosis of MI and CF may contribute to an improved survival as well. Prenatal diagnosis in families at risk provides an opportunity for early intervention and prevention of complications, possibly by reducing the extent of early and irreversible lung disease in the long term.[38] An additional advantage of early prenatal diagnosis is the prevention of the progression from simple to complicated cases. Fetal intestinal decompression has been attempted,[39] and amniography may be an invasive method of relieving intraluminal meconium obstruction in high MI risk cases in the future.

With regard to nutritional assessment, it has been difficult to predict the outcome of CF patients using the grading systems used to date.[3] Weight and height percentiles are used to evaluate children who have conditions interfering with normal growth such as malnutrition, and additionally, they can show the effects of various treatment modalities. It has been suggested that a deterioration of nutritional status in CF patients correlates with an increase in energy expenditure and a decrease in pulmonary function[40]; we posed the question as to whether nutritional outcome was affected by MI in the newborn period. Our data support a study of MI cases by Kerem et al,[41] in which long-term height and weight percentiles were below 50%, and their matched patient cohort showed no difference in growth percentiles between groups with or without MI. Our data show that surgical management of MI, even with limited bowel resection, does not seem to affect these patients' nutritional outcomes as compared with their peers with CF who do not have MI.

Conclusion

Short-term and long-term survival for MI patients has increased dramatically in the last three decades. The survival of MI patients past the newborn period seems to have been optimally affected by improved surgical and perioperative management, including the treatment of bacterial infection. Whether complicated or simple, survival has improved, independent of the surgical procedure. The BK ileostomy continues to be an effective and time-tested treatment for MI. Primary resection and anastomosis has less associated surgical morbidity, and can be used safely in complicated cases with discretion. The nutritional status of long-term MI patients has not been hampered by a complex newborn course that may include operation. The long-term survival of MI patients will be determined by their resistance to inevitable or irreversible pulmonary disease.

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