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Improving Poor Outcomes of Children With Biliary Atresia in South Africa by Early Referral to Centralized Units

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ABSTRACT

Objectives: Biliary atresia (BA) is a progressive fibrosing cholangiopathy of infancy, the most common cause of cholestatic jaundice in infants and the top indication for liver transplantation in children. Kasai portoenterostomy (KPE) when successful may delay the requirement for liver transplantation, which in the majority offers the only cure. Good outcomes demand early surgical intervention, appropriate management of liver cirrhosis, and in most cases, liver transplantation. These parameters were audited of children with BA treated at the Steve Biko Academic Hospital (SBAH) in Pretoria, South Africa.

Methods: All children with BA who were managed at SBAH between June 2007 and July 2018 were included. Parameters measured centered on patient demographics, timing of referral and surgical intervention, immediate and long-term outcomes of surgery, and follow-up management.

Results: Of 104 children treated, 94 (90%) were KPE naive. Only 23/86 (26%) of children were referred before 60 days of life and 42/86 (49%) after 120 days. Median time to surgical assessment and surgery was 4 (IQR 1–70) and 5 (IQR 1–27) days post presentation, respectively. The median age at KPE was 91 days (IQR 28–165), with only 4/41 (12%) of KPEs performed before 60 days of life. Of those with recorded outcomes, 12/33 (36%) achieved resolution of jaundice. Only a third of the cohort were referred for transplantation.

Conclusion: Children with BA have poor outcomes in the public health sector in South Africa. Late referrals, delayed diagnostics, advanced age at KPE with low drainage rates, poor follow–up, and low transplant rates account for low survival. Early referral to units offering expert intervention at all stages of care, including transplantation, would offer the best outcomes.

Key Words: Living donor liver transplants, end-stage liver failure

What Is Known

- Biliary atresia is a rare disease and an important cause of infantile cholestatic jaundice.
- The disease invariably progresses to end-stage liver failure.
- A Kasai portoenterostomy (KPE) may provide transplant-free survival, but most children with BA will require liver transplantation as destination therapy.

What Is New

- In a large proportion of patients, KPE will not achieve resolution of jaundice.
- Transplantation in children with no previous surgery and in a well-nourished state has less morbidity and mortality.
- Children in South Africa with BA do poorly, with or without a KPE, and should be referred to units offering transplantation at the earliest opportunity.

Biliary atresia (BA) is a serious progressive disease of the liver of unknown etiology. It represents the most common cause of neonatal cholestasis and pathologic direct hyperbilirubinemia (1).

The presentation of BA is nonspecific with cardinal features including conjugated hyperbilirubinemia beyond 14 days of age, acholic stools, hepatomegaly, dark urine, and failure to thrive (2). Late features of BA (after 80 days of life) include those of chronic liver disease and portal hypertension (3).

Several clinical entities may mimic BA, complicating the process of making an accurate and timely diagnosis (4). Only invasive testing (liver biopsy, intraoperative cholangiography, and histology of resected biliary duct remnant) will confirm BA (4). The disease may be suspected on clinical grounds alone and an ultrasound may confirm an underdeveloped or absent gallbladder (3).

The only potentially therapeutic modality to establish biliary drainage in the native liver is a KPE (1). It is recommended that a KPE be performed before 60 days of life, before liver cirrhosis becomes established (5). Primary transplantation may be considered failing performance of an early KPE (6,7) and in children with a late diagnosis (8).

The aim of this study was to analyze the referral patterns and subsequent management of children with biliary atresia at the Steve Biko Academic hospital (SBAH), in Pretoria, South Africa, to identify areas for improvement in obtaining destination therapy.

METHODS

Setting

SBAH is a public quaternary referral hospital in Tshwane (Pretoria), South Africa, attached to the University of Pretoria medical school. The department of pediatric surgery and pediatric

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gastroenterology are the only units providing follow-up services and work-up for transplantation for children with BA from a drainage population of 7 million people (9) with an average annual birth rate of 124 000 (10).

Study Design

A retrospective chart review of all children with BA who presented to SBAH for management, were performed during the time period from June 2007 to July 2018.

The data collected included patient demographics (gender and gestational age at birth and race), referral patterns to pediatric gastroenterology services at SBAH from referral hospitals in the area (age at referral in days) and referral patterns from gastroenterology to surgical services within SBAH (noting the time between referrals).

The data pertaining to KPEs were collected to demonstrate the number of procedures performed at the institution and rates of successful biliary drainage (defined as achieving a serum bilirubin level of <20 mmol/L at 6 months postprocedure). Factors potentially contributing to delays in providing surgical intervention were analyzed, including lack of theater time or intensive care beds availability. The rates of referral to other pediatric surgery units within the province, notably to the Chris Hani Baragwanath Academic Hospital, in the face of lack of resources, were recorded.

The rate of cholangitic episodes after KPE was noted and defined as the development of fever, abdominal pain, and deterioration of liver enzymes in a child with BA who had undergone a KPE. The utilization patterns of diagnostic imaging (including ultrasound, computerized tomography, magnetic resonance imaging , intraoperative cholangiography, and liver biopsy) were analyzed to determine its contribution to delay in definitive surgical management. The utilization of adjuvant medical therapy after KPE was recorded as well as follow-up patterns of patients. Last, referral patterns to transplantation services as well as transplantation rates were determined.

Data analysis consisted of descriptive statistics of the key factors, which spoke to the management of biliary atresia at SBAH.

The Ethics Committee of Faculty of Health Sciences Research, University of Pretoria, approved this study.

RESULTS

Patient Demographics and Referral Patterns to SBAH

A total of 104 children were treated for BA at SBAH over a 12-year period. The majority of children referred were KPE naive (94/104; 90%). The median age of referral within this group was at 112 days of life (IQR 8–400 days), with only 23/86 (26%) of children with recorded data reaching the unit before 60 days of life. Of the remainder within the KPE naive group, 42/86 (49%) reached specialist services at SBAH after 120 days of life and 21/86 (24%) between 60 and 120 days of life.

A proportion of patients 10/104 (9%) had undergone surgery at a neighboring institution and were referred to SBAH to access long-term gastroenterology follow-up and work-up for transplantation. The median age of referral within this group was 168 days (IQR 140–900 days) (Table 1).

Referral Patterns Between Specialties Within SBAH

A total of 104 children were assessed by the Department of Paediatric Gastroenterology over the 12 years in question. Within the KPE naive cohort, 59/94 (63%) were referred for assessment by the department of pediatric surgery and these patients were assessed for possible KPE within a median of 4 days (IQR 1–70 days). The remaining 35/94 (37%) of KPE naive patients were not referred for surgical assessment with the main reason being very late presentation to pediatric gastroenterology, all after 130 days of life (Fig. 1).

TABLE 1. Demographic characteristics of children with BA treated at Steve Biko Academic Hospital

Characteristic*	Median
Total number of children managed	104
Gender (N = 104), n (%)	
Female	60 (58)
Male	44 (42)
Gestational age at birth (N = 72), n (%)	
Term	67 (93)
Preterm	5 (7)
Race (N = 104), n (%)	
Black	101 (97)
White	3 (3)
Other	0 (0)

*Number of observations (N) vary between characteristics.
BA = biliary atresia.

Timing and Outcomes of KPE

When considering the group of patients assessed by the surgical team, 18/59 (30%) were not offered a KPE due to advanced cirrhosis being present on liver biopsy or on ultrasound findings which included the presence of a nodular liver, portosystemic shunts or reversed portal flow. In 3 cases, surgical intervention could not be offered in a timely manner and these patients were referred to the Chris Hani Baragwanath Academic Hospital, 50 km away. A total of 41 patients underwent KPE at SBAH, after clinical, intra-operative exclusion of advanced liver disease as indicated by the presence of varices or nodular liver parenchyma.

Surgery at SBAH was performed at a median of 5 days (IQR 1–27 days) after referral to pediatric surgery services. The median age at KPE was 91 days (IQR 28–165 days). Only 4/41 (12%) had a KPE performed before 60 days of life and 14/41 (35%) after 100 days of life. The KPE drainage rates, as evidence by the resolution of jaundice, were 12/33 (36%) within the cohort where results were available for analysis. A proportion of children 8/41 (20%) of children were lost to follow up, and the outcome of their surgery is unknown. The group of children who underwent KPE before the age of 90 days achieved biliary drainage at a slightly higher rate (6/14; 42%) than those who had operative intervention after 90 days of life (6/19; 31%).

All patients who had a KPE performed received adjuvant medical therapy consisting of corticosteroids, ursodeoxycholic acid, phenobarbitone, and prophylactic antibiotics.

Diagnostic Modalities Employed in Making the Diagnosis of BA

Ultrasound was utilized in all patients, intraoperative cholangiography was performed in 25/104 (24%) of patients, and liver biopsy in 78/104 (75%) of patients. A total of 10/104 (10%) of children underwent computerized tomography or magnetic resonance imaging performed and 18/104 (17%) underwent hepatobiliary iminodiacetic acid scanning (HIDA) (Table 2).

Endoscopic Surveillance of Varices and Rates of Cholangitis Post-KPE

The unit of pediatric gastroenterology had a very low threshold for surveillance endoscopy in all children who presented late (>120 days of life) and in those with clinical, biochemical, or radiological evidence of portal hypertension as evidenced by splenomegaly,

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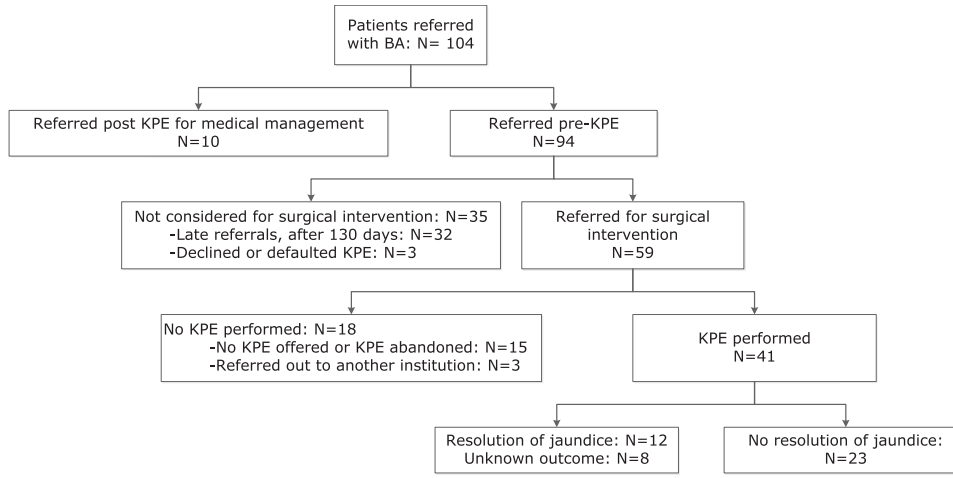


FIGURE 1. Study flow diagram of data on referral practices of children with BA to and within the Steve Biko Academic Hospital, from peripheral hospitals. BA = biliary atresia; KPE = Kasai portoenterostomy.

TABLE 2. Diagnostic modalities employed in the diagnosis of BA at Steve Biko Academic Hospital

Modality	Utilization rate
Ultrasound, N = 99, n (%)	99 (100)
IOC, N = 99, n (%)	24 (24)
HIDA scan, N = 99, n (%)	17 (17%)
CT/MRI, N = 99, n (%)	10 (10%)
Liver biopsy, N = 98, n (%)	76 (75%)

BA = biliary atresia; CT = computed tomography; IOC = intraoperative cholangiography; HIDA = hepatobiliary iminodiacetic acid scanning; MRI = magnetic resonance imaging.

thrombocytopenia, or nodular liver respectively. Within the cohort, 66/104 (63%) children received endoscopic surveillance for varices, of whom 49/66 (74%) developed evidence of portal hypertension (gastroesophageal varices and portal gastropathy).

Out of the group who underwent KPE, 34/59 (57%) had data available on the development of cholangitic episodes. Of those, 8/34 (24%) children had at least one episode of cholangitis.

Referral Patterns to Transplantation Units

A large proportion of children 57/104 (54%) did not undergo work-up for transplantation. In 36/57 (63%), the main reason for this was recorded as loss to follow up. Other reasons included death before work-up (8/57; 14%), social problems within the family (4/57; 7%), work-up declined by the family (3/57; 5%), fatal comorbidities (3/57; 5%).

Of the 47 children considered for transplantation, 15/47 (31%) were never referred to a transplant unit, mostly due to loss of follow-up. At the time of publication, 14/32 (43%) of the patients referred to the transplant unit had been transplanted (Fig. 2).

Of the 104 children managed with BA, 50 had incomplete records due to loss to follow up. Calculating the native liver survival proved difficult due to paucity of accurate data and poor follow-up of patients.

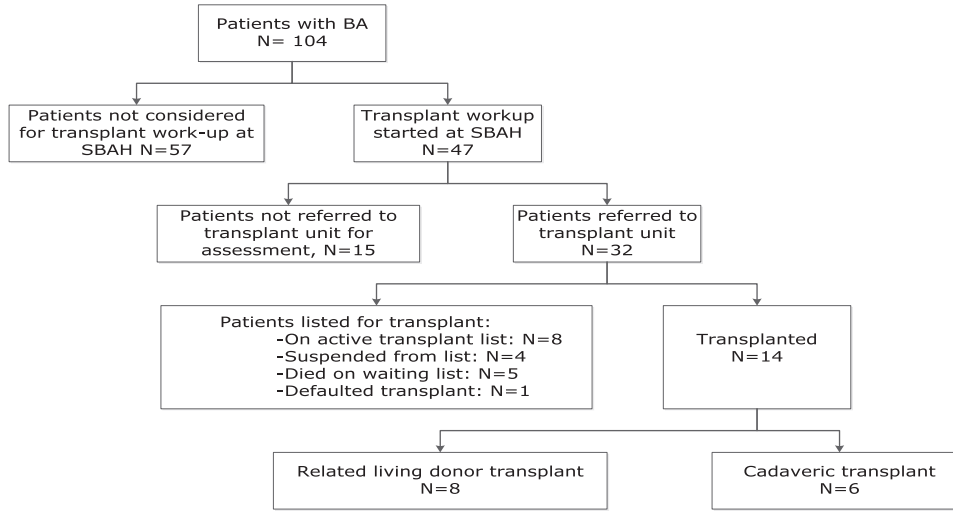


FIGURE 2. Study flow diagram of data on referral practices of children with BA for transplantation from the Steve Biko Academic Hospital. BA = biliary atresia; KPE = Kasai portoenterostomy.

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DISCUSSION

BA is a rare progressive cholangiopathy of childhood (1). The only available treatment is a KPE, which may successfully drain the biliary tree if performed in the early phases of the disease and in favorable anatomical subtypes (8). Even in the event of successful drainage, the majority will require liver transplantation for survival (7).

Early diagnosis, early referral to a tertiary center, timely Kasai, and appropriate postoperative management with work-up for transplantation are essential to ensure acceptable outcomes (3). Accurate unit data on referral practices and management is essential to ensure the appropriate outcomes for children with BA.

No data had previously been published on the treatment outcomes of children managed at SBAH in Pretoria, South Africa; a unit which provides pediatric gastroenterology and pediatric surgery services to several million people.

SBAH may be considered a medium to high volume center, receiving 10 cases of BA per year, and performing on average, 5 KPEs annually. Pediatric surgery centers (those performing > 5 KPE per year) report better outcomes than smaller centers (11). However, KPE at SBAH is performed relatively late and patients demonstrate low drainage rates postprocedure. These figures mirror results from other public South African pediatric surgery units (12). International consensus is that a jaundice clearance rate of 50% should be the benchmark for any center offering KPE with survival rates of 90% attainable in countries with access to liver transplantation (2), a goal yet to be attained for the majority of children with BA in South Africa.

Guidelines further recommend that a KPE be performed in children with BA before 60 days of life (5), to limit the extent of progressive fibrosis, which may limit the odds of achieving biliary drainage (8). In the face of very late referral and late access to specialized services, often in the presence of advanced liver disease, the opportunity to perform a timely KPE is curtailed. Patients who underwent an early KPE at SBAH (before 90 days of life) did achieve higher biliary drainage rates compared to those who did not.

Diagnostic work-up of the child with pathological jaundice should preferably occur within referral centers to avoid lengthy delays in obtaining results. Peripheral units should be encouraged to refer jaundiced children to tertiary institutions at the earliest opportunity.

At SBAH, ultrasound was the initial diagnostic modality of choice and a large proportion of children had a liver biopsy performed. It is important to note that waiting for histological confirmation in a patient with typical ultrasonographic and biochemical features of BA is not recommended (12), particularly in settings where the result of such a biopsy may only be available after 3–4 weeks, such as at the institution in question. The HIDA scan is rarely indicated and often of little value. It is very nonspecific and may also cause delays in definitive management. A small proportion of patients had an HIDA scan performed in this institution and this is currently discouraged within the department.

Referral between gastroenterology and pediatric surgery services within SBAH were not significantly delayed and access to theater time and intensive care beds were reasonable.

It was noted that a third of all patients seen by the pediatric gastroenterology unit were not referred for assessment by the surgical team at all, and referral to a transplant center were similarly low. KPE should be considered temporizing or palliative therapy, considering that survivors continue to develop fibrosis, cirrhosis, and portal hypertension and remain at risk of cholangitis and malignancy including hepatocellular carcinoma and cholangiocarcinoma (6). In reality, only 10%–15% of all children with BA will have symptom-free course even post-KPE (3). Access to a transplantation unit as part of the definitive treatment of BA is therefore critical.

Recent evidence strongly supports treating all children with BA in a centralized fashion in centers with access to transplantation as a therapeutic modality. These patients benefit from the concentration of resources as evidenced by the fact that these patients were prepared nutritionally and medically for transplantation from an early age (13–17)[5].

Only 45% of children were actively considered for transplantation and referral to the Wits Donald Gordon Medical Center in Johannesburg, the only unit offering living donor liver transplantation in South Africa and an even smaller proportion of children actually attended the transplant unit.

During the early years, liver transplantation was relegated to a salvage therapy due to high complication rates. Modern figures put 10 year survival after liver transplantation for BA at >90%. This raises the question whether transplantation should still be considered as salvage, or rather as the preferred primary therapy in some cases.

Potential limitations of this study include its retrospective uncontrolled nature. A large proportion of patients was lost to follow up and thus did not have sufficient data to interpret.

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