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Biliary atresia: the Brazilian experience

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Abstract

Objective: To evaluate epidemiological, clinical and prognostic characteristics of children with biliary atresia.

Methods: Data regarding portoenterostomy, liver transplantation (LTx), age at last follow-up and survival were collected from the records of patients followed up in six Brazilian centers (1982-2008) and compared regarding decades of surgery.

Results: Of 513 patients, 76.4% underwent portoenterostomy [age: 60-94.7 (82.6±32.8) days] and 46.6% underwent LTx. In 69% of cases, LTx followed portoenterostomy, whereas in 31% of cases LTx was performed as the primary surgery. Patients from the Northeast region underwent portoenterostomy later than infants from Southern ($p = 0.008$) and Southeastern ($p = 0.0012$) Brazil, although even in the latter two regions age at portoenterostomy was higher than desirable. Over the decades, LTx was increasingly performed. Overall survival was 67.6%. Survival increased over the decades (1980s vs. 1990s, $p = 0.002$; 1980s vs. 2000s, $p < 0.001$; 1990s vs. 2000s, $p < 0.001$). The 4-year post-portoenterostomy survival, with or without LTx, was 73.4%, inversely correlated with age at portoenterostomy (80, 77.7, 60.5% for ≤ 60, 61-90, > 90 days, respectively). Higher survival rates were observed among transplanted patients (88.3%). The 4-year native liver survival was 36.8%, inversely correlated with age at portoenterostomy (54, 33.3, 26.6% for ≤ 60, 61-90, > 90 days, respectively).

Conclusions: This multicenter study showed that late referral for biliary atresia is still a problem in Brazil, affecting patient survival. Strategies to enhance earlier referral are currently being developed aiming to decrease the need for liver transplantation in the first years of life.

J Pediatr (Rio J). 2010;86(6):473-479: Biliary atresia, portoenterostomy, hepatic, surgery, diagnosis, differential, prognosis.

Introduction

Biliary atresia (BA), characterized by obliteration of the extrahepatic bile ducts, remains the main indication for liver transplantation (LTx) in children.[1] BA clinical picture starts in the first weeks of life and displays a universal distribution with variable incidence in different regions of the world.[2-5] The etiology of BA remains elusive and several mechanisms have been proposed to explain its progressive cholangiopathy.[6,7] Early diagnosis of BA and surgical relief of the mechanical impediment to bile flow by portoenterostomy, preferably before 60 days of life, are

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crucial, since delay leads to the need for LTx or death in the first 3 years of life.[8-10] Prognosis of patients with BA has improved in the last decades, reaching 90% of cases,[10] due to timely performance of portoenterostomy and LTx followed by adequate immunosuppression. More than 50% of patients who undergo portoenterostomy become jaundice-free and, among them, several patients reach adolescence without LTx. For those who present complications such as portal hypertension and cirrhosis, LTx provides a good quality of life.[11] The experience of several countries regarding BA has been described,[5,12-17] but there are only a few isolated reports on the experience with BA in Brazil.[18,19] This study aimed to evaluate clinical, epidemiological and prognostic characteristics of Brazilian children with BA.

Patients and methods

Retrospective review of the medical records of patients with BA followed up between July 1982 and December 2008 in six Brazilian reference centers: Hospital de Clínicas de Porto Alegre at Universidade Federal do Rio Grande do Sul (UFRGS), South region; Hospital Sírio Libanês and Hospital do Câncer, São Paulo, Southeast region; Universidade Federal da Bahia (UFBA), Northeast region; Hospital de Base do Distrito Federal (HBDF), Midwest region; Universidade de Campinas (UNICAMP), Southeast region; and Universidade Federal de Minas Gerais (UFMG), Southeast region.

Data collected from the records included: sex; place of origin (Brazilian region) and category of town (capital city or countryside); birth weight; date of birth; onset of jaundice; hospital admission; presence of associated extrahepatic congenital anomalies; results from laboratory tests, ultrasound, biliary scintigraphy, biopsies from liver and *porta hepatis*; and surgical findings. Regarding therapy, data included the performance, or not, of surgical procedures (portoenterostomy and LTx) and date of procedures and postoperative outcomes, including date of last follow-up. Diagnosis of BA was based on clinical, biochemical, histological, imaging and surgical data, as previously reported elsewhere.[6,11]

Data were initially analyzed as a single set, being subsequently divided into three categories according to the decade in which portoenterostomy was performed: 1980s (1982-1989); 1990s (1990-1999); and 2000s (2000-2008). Age at portoenterostomy was classified according to four age groups: ≤ 60 days; 61-90 days; 91-120 days; and > 120 days. In order to analyze the overall and native liver survival, 91-120 days and > 120 days age groups were evaluated as a single group. Information was collected by investigators from each participating center and sent to the Data Registry Center, in Brasília, Brazil, where data were entered on a single platform for statistical analysis. Cases initially followed in a center and then transferred to another hospital to perform LTx were considered as a single case from only one of these centers. Since this was a retrospective study, a complete data collection including all patients was not feasible.

Categorical variables were described in figures and tables of frequency distributions, and continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile (IQ) range. The chi-square test and Student's *t* test were used for comparisons. Survival curves were built using the Kaplan-Meier method and the Cox model and compared by calculating the hazard ratio. Overall survival was based on date of birth and date of death or last follow-up. Native liver survival was based on date of birth, LTx, and death or last follow-up. P values < 0.05 were considered to be statistically significant. Microsoft Excel 2007 (Microsoft Corp, Redmond, WA, USA) and SPSS 15.0 (SPSS Inc, Chicago, IL, USA) were used for data processing and statistical analysis.

This study was approved by the Research Ethics Committees of the participating institutions.

Results

Data on patients with BA (n = 513, 283 female and 230 male) included in this study were sent by individual centers to the Data Registry Center, in Brasília, Brazil. The number of patients according to individual centers was: 187 (36.5%), UFRGS; 151 (29.4%), Hospital Sírio Libanês and Hospital do Câncer; 63 (12.3%), UFBA; 53 (10.3%), HBDF; 37 (7.2%), UNICAMP; and 22 (4.3%), UFMG. Distribution of patients according to Brazilian regions was: 185 (36.1%), South; 169 (32.9%), Southeast; 96 (18.7%), Northeast; 50 (9.8%), Midwest; and 13 (2.5%), North. Forty-five (8.8%), 133 (25.9%) and 335 (65.3%) patients were admitted in the 1980s, 1990s and after 2000, respectively.

Mean birth weight of patients was 3,138.6 (±499.3) grams and the onset of jaundice occurred at 12.3 (±17.0) days of life. Extrahepatic congenital anomalies were found in 61 (11.8%) patients, including splenic (n = 10), gastrointestinal (n = 25), cardiovascular (n = 25), urinary (n = 6), and teratoma (n = 1) anomalies. Six patients had more than one anomaly. Findings suggestive of BA splenic malformation syndrome occurred in 17 patients, including polysplenia (n = 5), abdominal *situs inversus* (n = 11), and dextrocardia (n = 1).

Blood chemistry measurements were: total bilirubin, 11.9 (±6.2) mg/dL; serum direct bilirubin, 9.1 (±5.8) mg/dL; gamma-glutamyltransferase (GGT), 15.2 times the normal value (x N) (±16.4); aspartate aminotransferase (AST), 6.1 x N (±4.7); and alanine aminotransferase (ALT), 4.7 x N (±4.8). Regarding liver histopathology, most patients had bile plugs (93.8%), ductular/ductal proliferation (93.8%), and fibrosis (84.1%). Since this was a retrospective study,

a complete data collection including all patients was not feasible, and results of biliary scintigraphy and abdominal ultrasound, among other tests, could not be analyzed.

Portoenterostomy

Portoenterostomy was performed in 392 (76.4%) patients; among these, for 12 patients age at portoenterostomy could not be determined (Figure 1). These patients underwent LTx and their post-transplant follow-up data were available for analysis. Age at portoenterostomy for the remaining 380 patients was 82.6±32.8 days [median = 78.5 (60.0-94.7) days].

Only 100 (26.3%) patients were operated on until 60 days of life. Most (45.0%) patients underwent portoenterostomy between 61 and 90 days, 79 (20.8%) patients were operated on between 91 and 120 days, and 30 (7.9%) patients after 120 days (Table 1). An increasing number of patients underwent portoenterostomy in the subsequent decades under study. When comparing the three decades with regard to age at portoenterostomy, there were increasing rates of patients undergoing the procedure between 61 and 90 days of life (p = 0.047) and decreasing rates after 120 days (p = 0.020).

When comparing the rates of patients undergoing or not portoenterostomy according to their distribution across Brazilian regions (Table 2), most non-operated infants were from the North (69.2%) and Northeast (45.8%), while only 11.9% of patients were from Southern Brazil. Regarding category of town, capital city or countryside, no significantly different rates were observed (24.8 vs. 23.0%).

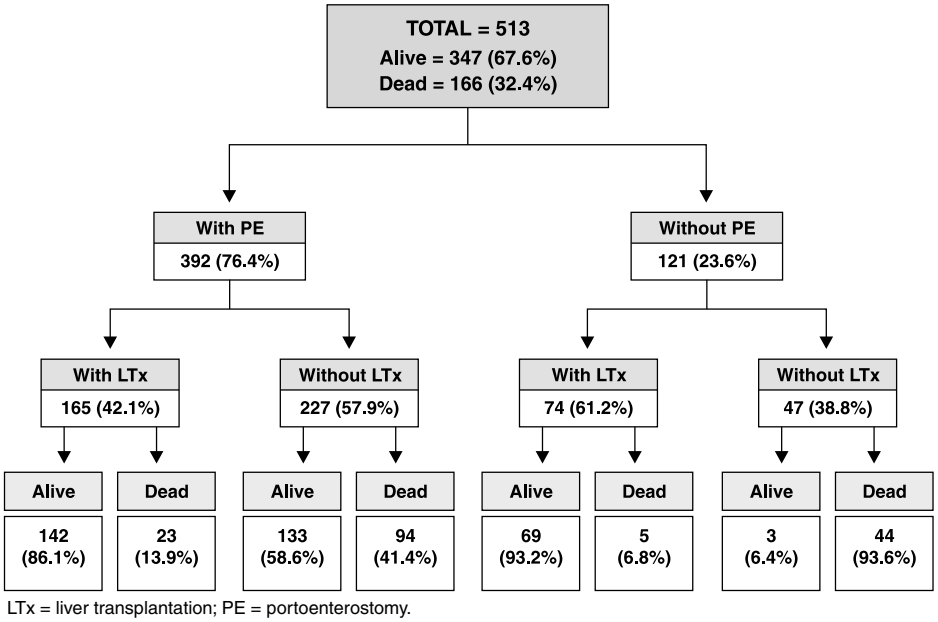
Regarding age at portoenterostomy, according to Brazilian regions (Table 2), infants from the Northeast and North were operated on later [92.3 (±36.1) and 102.2 (±36.4) days, respectively] than infants from the Midwest [84.9 (±29.9) days], South [80.8 (±36.6) days] and Southeast [79.5 (±25.4) days]. Age at portoenterostomy was significantly different when South and Northeast regions (p = 0.008) and Southeast and Northeast regions (p = 0.012) were compared. However, there were no differences when other regions were compared or when patients from capital cities [82.2 (±35.9) days] and from countryside [82.8 (±31.3) days] were compared (p = 0.639).

Liver transplant

Of all patients, 239 (46.6%) underwent LTx. A comparison over the three decades revealed increasing rates of performance of LTx in Brazil (1980s vs. 1990s, p = 0.016; 1980s vs. 2000s, p < 0.001; 1990s vs. 2000s, p < 0.001), as described in Table 1. In 69.0% of cases, LTx followed portoenterostomy, whereas in 31.0% of cases LTx was performed as the primary surgery (Figure 1). Among patients previously subjected to portoenterostomy, age at LTx ranged from 0.8 to 2.6 (2.6±3.1) years. The remaining children were transplanted earlier, at around 0.6-1.5 (1.2±0.8) years, revealing a significant difference between groups (p < 0.001).

Survival rates

The overall survival was 67.6%, and the highest survival rates occurred in transplanted patients (without previous



LTx = liver transplantation; PE = portoenterostomy.

Figure 1 - Follow-up of the study sample with biliary atresia (n = 513)

Table 1 - Comparison over decades of performance of portoenterostomy, age at procedure, survival rates and performance of liver transplantation

	Decade			
	1980s n (%)	**1990s n (%)**	**2000s n (%)**	**Overall n (%)**
Age at PE (days)				
≤ 60	10 (25.0)	31 (27.9)	59 (25.7)	100 (26.3)
61-90	14 (35.0)	46 (41.5)	111 (48.5)	171 (45.0)
91-120	8 (20.0)	23 (20.7)	48 (21.0)	79 (20.8)
>120	8 (20.0)	11 (9.9)	11 (4.8)	30 (7.9)
Total	40 (100.0)	111 (100.0)	229 (100.0)	380 (100.0)
Outcomes				
Survival*	13 (28.9)	74 (55.6)	260 (77.6)	347 (67.6)
Performance of LTx†	7 (15.6)	46 (34.6)	186 (55.5)	239 (46.6)
Total of patients	45 (8.8)	133 (25.9)	335 (65.3)	513 (100.0)

LTx = liver transplantation; PE = portoenterostomy.
* Between decades: 1980s vs. 1990s, p = 0.002; 1980s vs. 2000s, p < 0.001; 1990s vs. 2000s, p < 0.001.
† Between decades: 1980s vs. 1990s, p = 0.016; 1980s vs. 2000s, p < 0.001; 1990s vs. 2000s, p < 0.001.

portoenterostomy, 93.2%; with previous portoenterostomy, 86.1%). The highest mortality rates occurred in non-operated patients (93.6%), among which only 3 children (6.4%), all younger than 2 years, remain alive (Figure 1). The overall survival of transplanted patients (88.3%) was higher than that of non-transplanted patients (49.6%, p < 0.001). Table 1 shows increasing overall survival rates over the three decades under study (1980s vs. 1990s, p = 0.002; 1980s vs. 2000s, p < 0.001; 1990s vs. 2000s, p < 0.001).

The 4-year post-portoenterostomy survival, including patients that eventually underwent LTx, was 73.4%. Figure 2A shows that 4-year survival was inversely correlated with age at surgery, with rates of 80.0, 77.7 and 60.5% in children operated at ages ≤ 60 days, 61-90 days, and > 90 days, respectively. Within the group of children operated at

Table 2 - Rates and age of patients undergoing portoenterostomy according to place of origin (Brazilian region and capital city or countryside)

	Place of origin						
Portoenterostomy	**South**	**Southeast**	**Midwest**	**Northeast**	**North**	**Capital**	**Countryside**
Yes, n (%)	163 (88.1)	133 (78.7)	40 (80.0)	52 (54.2)	4 (30.8)	121 (75.2)	271 (77.0)
Total, n (%)	185 (100.0)	169 (100.0)	50 (100.0)	96 (100.0)	13 (100.0)	161 (100.0)	352 (100.0)
Age (days)							
Mean	80.8†	79.5*	84.9	92.3*†	102.2	82.2	82.8
±SD	±36.6	±25.4	±29.9	±36.1	±36.4	±35.9	±31.3
Median	74.0	77.0	80.5	90.0	103.0	79.0	77.5
Min-max	59.0-93.0	60.0-90.0	60.7-102.0	70.7-120.0	66.7-137.0	60.0-92.0	60.0-96.0

Max = maximum; min = minimum; SD = standard deviation.
* p = 0.012.
† p = 0.008.

age > 90 days, there was a significant difference when the 4-year post-portoenterostomy survival rate was compared to that of other age groups (≤ 60 days and 61-90 days) (p = 0.003).

Native liver survival ranged from 0.8 to 3.2 (3.24±4.48) years. Among patients who died, it ranged from 0.8 to 1.7 (2.0±3.0) years; in transplanted patients, from 0.7 to 2.0 (2.1±2.7) years; and in patients who remain alive with their native liver, it ranged from 1.3 to 10.7 (6.4±6.2) years.

Figure 2 shows that 4-year native liver survival reached 36.8% of cases and was inversely correlated with age at portoenterostomy: 54.0% in children operated on until 60 days of life, 33.3% in those operated on between 61 and 90 days, and 26.6% in patients operated on after 90 days, with significant differences between age groups (≤ 60 vs. 61-90 days, p = 0.006; ≤ 60 vs. > 90 days, p = 0.001).

Discussion

This study comprises a large series of children with BA, including patients from all Brazilian regions, and evaluates data regarding portoenterostomy, LTx, and survival. In this series there was a slight predominance of female infants (1.2:1.0), in agreement with the literature,[20] and a low rate of associated congenital anomalies (12.0%), indicating, as observed in other studies,[21] the prevalence of the perinatal form of BA.

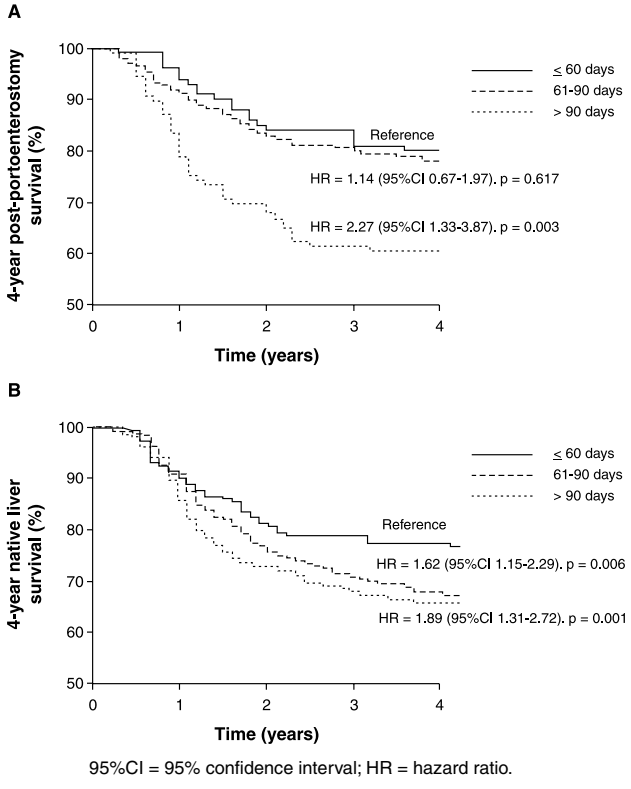


Figure 2 - Four-year survival and 4-year native liver survival according to age at portoenterostomy. A) 4-year survival curve. Log rank (Mantel-Cox) = 13.99, p = 0.001; B) 4-year native liver survival curve. Log rank (Mantel-Cox) = 13.38, p = 0.001

This investigation showed that, currently in Brazil, most patients are not operated as needed or undergo late portoenterostomy, after 60 days of life, a situation that can negatively affect their native liver survival. The observed age at portoenterostomy, which was higher than desirable, reveals the occurrence of late referral, a problem that has been previously described in our country.[18,19] Thus, in Brazil, late referral of patients with BA for portoenterostomy remains a problem to be solved nationwide, regardless of region and category of town, whether capital city or countryside. Early patient referral for portoenterostomy in due time remains a challenge worldwide,[22-26] but it has been attained in some countries,[27] with a trend toward decreasing age of referral over the years. In developed countries, age at portoenterostomy is around 60 days.[13,14,28]

The 4-year survival rate among Brazilian patients who underwent portoenterostomy (73.4%) was similar to that observed in other centers, such as in Canada (79.0%)[5] and France (75.3%).[13] The 4-year native liver survival rate of Brazilian patients (36.8%) was similar to that of patients from Canada (36.0%)[5] and Switzerland (37.4%),[15] but lower than that observed in the United Kingdom (51.0%)[14] and Japan (63% in 5 years).[28]

In this study, 4-year survival rate and 4-year native liver survival rate were both inversely correlated with age at portoenterostomy, reinforcing the detrimental effect of age on the postoperative prognosis.[8,26,29] Age at portoenterostomy is known to affect native liver survival. According to Serinet et al.,[30] its impact remains until adolescence and, if all patients with BA underwent portoenterostomy before 46 days of life, 5.7% of all LTx performed in France in patients younger than 16 years could be avoided. The best surgical results are reached when the procedure is performed within the first 30 days of life.[5] It is still debatable whether portoenterostomy should be performed in patients older than 90 days of life. In this study, the 4-year native liver survival in patients operated later, after 90 days, was 26.6%, similar to that observed in Canada (23.0% in 4 years)[5] and France (25.0% in 5 years).[31] Furthermore, in the United Kingdom, the 5-year native liver survival rate of patients operated on after 100 days reached 45.0%.[32] Such data suggest that portoenterostomy should be attempted even in children around 90 days of life, provided they present neither decompensated liver disease nor complications of portal hypertension.

The importance of portoenterostomy is evidenced in Figure 1, which shows a mortality rate of 41.4% for operated infants, not subjected to LTx, in comparison with patients who did not undergo any procedure (93.6%). Portoenterostomy

can provide a 20-year native liver survival for 21.0% of patients,[33] while native liver survival of non-operated children with BA decreases dramatically in the first years of life.[13] In the long run, however, most patients with BA ultimately need a LTx.[34] In this study, 46.6% of patients underwent LTx, a low rate in comparison with other countries, such as Switzerland (64.6%)[15] and Canada (60.0%).[5] The low LTx rates observed herein may reflect socioeconomic and cultural difficulties of the population in some Brazilian regions, in which access to centers where LTx is performed is not always feasible. On the other hand, LTx was the first surgical therapy in 31.0% of patients, a rate higher than that observed in other centers,[2,4,13-15,26,33] which may reflect the late referral for diagnosis of BA. Patients who underwent portoenterostomy were transplanted later (2.6±3.1 years) than children not undergoing the procedure (1.2±0.8 years) ($p < 0.001$), suggesting that it is worth performing portoenterostomy as the first-choice surgical treatment. Although portoenterostomy can not alter the number of LTx in patients with BA throughout life, it can postpone its performance.[35] In developed countries, sequential performance of portoenterostomy and LTx leads to overall survival rates around 90.0%,[36] higher than that observed in this study (67.6%). However, increasing survival rates have been observed over the last three decades, reaching a rate of 77.6% in the last decade, a number similar to that obtained in Canada[5] and Japan.[2] These higher survival rates coincided with increasing LTx performance due to the collaborative efforts of some centers, included in the Brazilian public Unified Health System, where LTx is performed. Figure 1 shows that performance of LTx reduced mortality rates among Brazilian children with BA, with a post-transplant survival reaching 88.3%, a rate similar to that observed in Canada,[5] USA,[12] and United Kingdom.[35] Another factor that may negatively impact overall survival rates, in addition to availability of LTx, is late referral of patients with BA. In Brazil, late referral of patients with BA might reflect difficult access to reference centers or lack of diagnostic suspicion by parents and non-specialized pediatric services, since, at onset, patients are in good condition and present appropriate weight for age. Jaundice, which may be less evident, mainly in dark-skinned patients, can be overlooked, thus delaying diagnosis. Experiences from other countries have proved that late referral can be changed by improving medical practices and health policies. The United Kingdom adopted a policy of centralization in 1999, limiting treatment of patients with BA to three reference centers,[14] while France, in 1997, introduced a collaborative effort among their various national centers.[13] Other countries have adopted measures to raise awareness of their population with warning signs and screening systems for BA, such as "Yellow Alert" campaigns[37] and the use of a colorimetric scale to identify acholic stools.[38,39] Among these strategies, the national stool color screening system, which integrated the infant stool color card into the Child-health Booklet given to every neonate, has proven to be effective and easily applicable.[40]

In summary, this multicenter study on patients with BA showed that, in Brazil, overall survival of affected patients is below the desired level already attained by other groups, but post-transplant results are similar to those attained in developed countries. However, the number of LTx is still below demand. A timely performance of portoenterostomy increases postoperative survival rates, decreasing the need for LTx in the first years of life. Late referral of patients with BA remains a nationwide problem in Brazil. Currently, Brazilian pediatric hepatologists involved in the treatment of patients with BA are trying to develop collaborative strategies in order to improve the situation of affected children. These professionals, in concert with the Brazilian Society of Pediatrics, have included the stool color card into the Child-health Booklet distributed by the Brazilian Ministry of Health to parents of every neonate and launched a national "Yellow Alert" campaign to raise awareness of parents and pediatricians about the problems of neonatal cholestasis. Additionally, a Brazilian BA research consortium, following the American BARC, was created to produce multicenter collaborative studies on BA etiology, therapeutics and prognosis. This may be the dawn of a new era in the management of BA in Brazil, through the development of such collaborative efforts. The die is cast!

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