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A review of the literature on childhood Burkitt lymphoma in Nigeria

DOI:<http://dx.doi.org/10.4314/njp.v43i1.1>

Accepted: 8th December 2015

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Abstract: *Background:* Burkitt Lymphoma is common childhood tumour in sub-Saharan Africa but the lack of centralized database on childhood cancer in Nigeria has made it difficult having a nationwide picture of its occurrence in the country.

Objectives: This study was aimed at pooling published data from across the country with the hope of providing an overview of the profile of the disease in Nigeria.

Methods: literature search was carried out on Pub Med/MEDLINE and Cochrane databases for all articles published between January 1975 and July 2015 using search strings such as children, cancer, Burkitt's, epidemiology, prevalence, treatment and Nigeria. Based on specific criteria, 39 studies were included.

Results: Burkitt Lymphoma was the most common childhood malignancy in most parts of the country accounting for 18.3-65.0% of malignant tumours but a few centers observed Retinoblas-

toma as the most common. There was a decline in the frequency of Burkitt lymphoma in Ibadan from 1960-2010 and in Lagos. Peak ages of occurrence ranged from 5-10 years, more males and children from low socio-economic classes were affected. Different centers reported predominant involvement of either the jaw or the abdomen but there were slightly more centers with predominance of the jaw. Retrospective studies yielded an estimated survival of 15-23% while the Event Free Survival probabilities at two years was 43% and 48% for the Nigerian centers that participated in an international study.

Conclusion: Burkitt Lymphoma is a common tumour in Nigeria. Establishment of Cancer registries for better data capture and funding for better treatment outcomes is recommended.

Key words: Burkitt Lymphoma; Nigeria; childhood; tumours; cancer

Introduction

Burkitt lymphoma is an aggressive B cell Non-Hodgkin's lymphoma characterized by a high degree of proliferation of the malignant cells and deregulation of the *c-MYC* gene¹. It has three variants namely the endemic, sporadic and HIV –associated forms². The highest incidence of the endemic form occurs in the lymphoma belt lying between latitude 10 degrees north and south of the equator and characterized by malaria holoendemicity². It is therefore common in Tropical Africa and in Papua New Guinea³.

Endemic Burkitt lymphoma refers to those cases occurring in African children, usually 4–7 years old, involving the bones of the jaw and other facial bones, as well as kidneys, gastrointestinal tract, ovaries, breast, and

other extranodal sites⁴. Epstein Barr virus (EBV) is found in nearly all cases. Sporadic Burkitt lymphoma occurs worldwide; with no specific geographic or climatic association. It accounts for 1%–2% of lymphoma in adults and up to 40% of lymphoma in children in the United States⁵. The abdomen, especially the ileocecal area, is the most common site of involvement; other sites that may be involved include the ovaries, kidneys, omentum, and Waldeyer's ring. Only about 15% of cases of sporadic Burkitt Lymphoma harbor the EBV genome⁶. Immunodeficiency-associated Burkitt lymphoma occurs mainly in patients infected with HIV but has also been reported in organ transplant recipients⁷.

Nigeria is the most populous country in Africa and the country's 2006 Population and Housing Census placed the country's population at 140,431,790⁸. It is divided into a Federal Capital Territory and thirty-six states and

the states are divided into six geopolitical zones: North-West, North-East, North-Central, South-East, South-South, and South-West. The country lies on the west coast of Africa between latitudes 4°16' and 13°53' north and longitudes 2°40' and 14°41' east and therefore falls within the lymphoma belt⁸. Burkitt lymphoma is therefore expected to be common in Nigeria, given its geographical location. Studies from several states of the country report Burkitt Lymphoma to be the most common type of cancer in children⁹⁻¹¹ but a few have reported the contrary^{12,13}. A centre within the country has reported a downward trend in the relative frequency of Burkitt Lymphoma with respect to other tumours but this has not been appraised in most parts of the country¹². In terms of clinical presentation, whilst some centres have reported the jaw or face as the predominant site affected^{11,14}, others have reported the abdomen as the most common site^{15,16}.

Incidentally, there is no national cancer registry or database to provide a general view of the situation nationwide. There is also paucity of population based Cancer registries and many of publications on childhood cancer are based on reports from Pathology departments or clinical reviews. There is therefore lack of national incidence data for the disease which could serve as baseline data and guide policy formulation towards management and control. This is important given the association of the tumour with malaria and therefore the potential to control its occurrence with malaria control measures². The aim of this study was to compile published data on Burkitt lymphoma across the country in order to summarize them and provide an overview of the national pattern of the disease. The objectives of this study were to describe the relative frequency, socio-demographic features, predominant clinical sites of involvement and treatment outcomes of Burkitt lymphoma in Nigeria. The ultimate aim was to provide a summarized report that could serve as a proxy for generalizable data in the absence of a centralized database for childhood cancer. In addition, it was hoped that any regional differences in pattern would be highlighted by this review.

Methodology

This was a review of published scientific literature on Burkitt lymphoma in Nigeria between January 1975 and July 2015. Literature search was performed on PubMed / MEDLINE and Cochrane databases for all articles using search strings or key words such as children, cancer, Burkitt's, epidemiology, prevalence, treatment and Nigeria. The reference list of articles were also checked for other articles that were not detected by the bibliographic search. The inclusion criteria for each analysis depended on the specific objective targeted by that analysis. In general, only studies based on cases from cancer registries or histopathology departments or clinical studies confirmed histologically or cytologically were included. For analysis of relative frequency of Burkitt lymphoma, emphasis was placed on studies in-

volving all childhood malignancies including leukemias and solid tumours. Studies that were based on solid tumours alone were analyzed separately and the ranking of Burkitt lymphoma stated but frequency figures downplayed since they would not be representative of the entire spectrum of childhood tumours.

A total of 39 articles on Burkitt Lymphoma in Nigeria were reviewed. Sixteen studies were from the south west zone constituting the majority, followed by the North West, south east and north central zones with 8, 7 and 6 studies respectively while the south-south and north east zones had two and one articles respectively¹, one article was based on 2 centres). Clinical or clinic-pathologic studies were used for analysis of socio-demographic features and predominant sites of tumour involvement and in this regard, emphasis was placed on studies that included all tumours confirmed either by cytology of fine needle aspirate or histology from a surgical biopsy. Studies based exclusively on surgical biopsy specimen were analyzed separately and given less emphasis because the usual method of diagnosing Burkitt lymphoma in Africa is through cytology of fine needle aspirates of accessible tumour and so analyzing only studies based surgical biopsies is likely to exclude a significant proportion of cases and therefore introduce bias to the results¹⁷.

For centres with multiple publications on Burkitt lymphoma over time, the most recent was used for prevalence figures. However, for analysis of trend, all studies that met the inclusion criteria over time were used.

Results

Prevalence

Ten centres reported relative frequency of Burkitt lymphoma among all cases of childhood malignant diseases confirmed cytologically or histologically (Table 1). Burkitt lymphoma was the commonest in eight of the centres namely Enugu, Zaria, Jos, Ekiti, Calabar, Saganu, Abia and Gwagwalada with prevalence ranging from 18.3 to 65.0% of malignant tumours of child hood in the various centers^{9-11,18-22}. These centres are spread across the FCT and five geopolitical zones but excluding the north east geopolitical zone. Retinoblastoma was the most common tumour in two centres namely, Ibadan and Kano with Burkitt lymphoma being the second most common cancer in both cities^{12,13}.

Studies from seven centres were restricted to solid tumours; Burkitt lymphoma was the most common solid tumour in four centres namely Sokoto, Ilorin, Port Harcourt and Ile-Ife as shown in table 2²³⁻²⁶. In the fifth centre, Zaria, Burkitt Lymphoma and Retinoblastoma were of equal frequency and ranked highest²⁷. Out of the remaining two centres, Jos reported Rhabdomyosarcoma as the predominant solid tumour accounting for 31 percent of the tumours with Burkitt Lymphoma being the third most common and accounted for 13.8 percent of the tumours while in Lagos, Retinoblastoma was reported to be the predominant tumour and accounted

for 21% of the tumours whereas Burkitt Lymphoma accounted for only 2% of the tumours^{28,29}.

Table 1: Frequency of Burkitt Lymphoma among all childhood cancers in different cities of Nigeria

Study	Year of Publication	City/State	Geopolitical Zone	Most Common cancer	Sample size	Frequency of Burkitt Lymphoma %	Data Source
Ekanem ¹⁹	1992	Calabar	South south	Burkitt Lymphoma	60	18.3	Ward admissions
Ocheni ⁹	2005	Enugu	South east	Burkitt Lymphoma	79	24.1	Cancer Registry
Agboola ¹⁸	2009	Sagamu	South west	Burkitt Lymphoma	77	36.0	Pathology department
Mohammed ¹⁰	2009	Zaria	North west	Burkitt Lymphoma	329	27.0	Cancer registry/ hospital records
Awolola ²⁰	2011	Ekiti	South west	Burkitt Lymphoma	28	28.6	Pathology department
Okpe ¹¹	2011	Jos	North-central	Burkitt Lymphoma	92	48.9	Ward admissions
Ochicha ¹³	2012	Kano	North west	Retinoblastoma	438	19.9	Pathology and Haematology Laboratories
Offiong ²¹	2012	Abuja	Federal Capital Territory	Burkitt Lymphoma	46	43.5	Ward admissions
Babatunde ¹²	2015	Ibadan	South west	Retinoblastoma	625	11.7	Pathology department
Chineke ²²	2015	Abia	South east	Burkitt Lymphoma	40	65.0	Clinical/pathology department

Table 2: Frequency of Burkitt Lymphoma among childhood solid malignant tumours in different cities

Study	Year	City/State	Geopolitical Zone	Patient population	Tumour spectrum	Commonest cancer	Sample size	Frequency of Burkitt Lymphoma %	Data Source
Adelusola ²⁶	1995	Ile-Ife	South-west	Hospital-based	All solid tumours	Burkitt Lymphoma	157	69.0	Pathology department
Seleye-Fubara ²⁵	2005	Port Harcourt	South-south	Hospital-based	All solid tumours	Burkitt Lymphoma	173	41.6	Pathology department
Malami ²³	2005	Sokoto	North-west	Hospital-based	All solid tumours	Burkitt Lymphoma	158	35.5	Pathology department
Samaila ²⁷	2009	Zaria	North-west	Hospital-based	Histologically diagnosed cases only	Burkitt Lymphoma & Retinoblastoma	189	14.3 each	Pathology Department
Akinde ²⁹	2009	Lagos	South-west	Hospital-based/ outside	Histologically diagnosed cases only	Retinoblastoma	274	2.0	Pathology department
Tanko ²⁸	2009	Jos	North-central	Hospital-based	Histologically diagnosed cases only	Rhabdomyosarcoma	181	13.8	Cancer registry
Omotayo ²⁴	2013	Ilorin	North-central	Hospital-based	Histologically diagnosed cases only	Burkitt Lymphoma	261	44.4	Pathology department

All solid tumours = diagnosed from cytology of fine needle aspirate and histology of tissue biopsy

Trend in relative frequency of Burkitt Lymphoma

A review by Ojesina *et al*³⁰ observed a decline in prevalence in Ibadan from 51.5% in the period 1960 to 1972 reported by Williams³¹, to 37.1 % in the period 1973 to 1990 reported by Akang³² and subsequently 19.4% in the period 1991-1999 reported by Ojesina *et al*³⁰. The 11.7% reported by Babatunde *et al* for the period 1991-2010 confirms a consistent decline in the relative frequency of Burkitt lymphoma in Ibadan over time¹². Similarly, a decline in the frequency of Burkitt Lymphoma among solid tumours has been reported in Lagos; from 19.6% reported by Tijani *et al*³³ in the period between 1974 and 1978 in which it ranked first through, 9.5% reported by Akinsulie *et al*³⁴ in the period 1988-1998 in which it ranked third to, 2% reported by Akinde *et al*²⁹ for the period 2000-2007.

In Enugu, South eastern Nigeria, Ocheni *et al*³⁵ reviewed the relative frequency of Burkitt lymphoma over four time periods. The relative frequency of Burkitt lymphoma was 37% between 1976-80 reported by Agugua and Okeahialam³⁶, 26.5% between 1978-82 reported by Obioha *et al*³⁷, 25.3% from 1989-98 reported by Onwasigwe *et al*³⁸ and 24.1% between 1999-2004 reported by Ocheni *et al*³⁵. Considering the period between 1978 and 2004, there does not seem to have been an appreciable change in the frequency of Burkitt

Lymphoma in Enugu.

Age distribution

Fifteen studies described peak ages of occurrence of Burkitt Lymphoma in children while two studies that included children and adults described median ages. Out of the fifteen studies on children, fourteen spread across all geopolitical zones reported peak ages of 5-10 years (10,11,13-16,19,22,23,25,27,30,39-41). Only one study on children, from Sagamu reported a peak age of 1-5 years (18). Out of the two studies that included children and adults, Kagu *et al*⁴² in Ile-Ife reported a median age of 9 years while Obafunwa and Akinsete reported a median age of 10 years⁴³.

Sex distribution

Fifteen studies from nine centres across northern and southern Nigeria described the sex distribution of patients with Burkitt lymphoma and all reported male predominance with a male: female ratio ranging from 1.2-2.7: 1(10,13-16,19,22,23,27,30,39-42,44,45).

Socio economic status

Studies on Burkitt Lymphoma in Nigeria that have de-

scribed the socio economic status of children have usually reported that parents of majority of affected children belong to the low socio economic class (SEC) but reporting format has also lacked uniformity for summarization or comparability. In a retrospective study in Ibadan, south west Nigeria, by Aderele and Antia: out of 133 children studied, occupation of 121 fathers was available- 42% were subsistence farmers fathers with no formal education, 20% were traders while 37% were artisans like carpenters, drivers, tailors or casual labourers, only one father an assistant superintendent of Police had a relatively high income¹⁵. A prospective study by the same authors, revealed that none of the children belonged to the high social class but most of the patients were from the lowest socio-economic classes including 58% from class V, the lowest social class⁴⁶. Oguonu *et al*¹⁶ in Enugu, south eastern Nigeria, reported that 89% of children with Burkitt lymphoma lived in rural areas and most patients belonged to the low SEC 75% of them being from the lowest socio economic class and 54% of parents illiterate. Another study from south eastern Nigeria, by Chinekeet *al*²² revealed that 61.5% of Burkitt Lymphoma patients in Abia state were from a low socio-economic class. Ibrahim *et al*⁴¹ in Sokoto reported that all parents in their study belonged to the low income groups, none had formal education and all mothers were housewives. In summary, most of the parents were of the low socioeconomic class and this ranged from 61.5 to 100% of patients where figures are stated.

Clinical presentation

Eleven studies from nine centres that described the clinical features of patients with Burkitt Lymphoma were studied out of which the jaw was the predominant site affected in five studies while the abdomen was the predominant site in the remaining six studies. The six studies in which the abdomen was the predominant site include two from Ibadan, and one each from Enugu, Jos, Zaria and Sokoto in which the abdomen occurring either alone or in combination with other sites accounting for between 32 and 77.8 % of tumours(15,16,39,41,43,47). The five studies in which the jaw was the predominant site affected include one each from Abia State, Maiduguri, Ile-Ife, Calabar and Jos; the jaw accounted for between 40.7 and 77 % of cases seen occurring either alone or in combination with other sites (11,14,19,22,42). The study from Jos that had the abdomen as the predominant site was published in 1992

while that which had the jaw as the predominant site was published in 2011. Therefore, using the more recent data from each centre with multiple figures, the jaw was predominant in five centres and the abdomen in four out of the nine centres studied.

Treatment

Seven studies that met the inclusion criteria described treatments given comprising six local studies and one international multicenter study. The international study was included because although it involved three African countries, survival rates for the Nigerian centres were presented separately. The local studies were all retrospective and each used a variety of treatment regimens but the predominant regimens used in each study are shown in table 3. The most commonly used regimen consisted of Cyclophosphamide, Oncovin and Methotrexate (COM). Other drug treatments given included Cyclophosphamide, Methotrexate and prednisolone¹⁶, monotherapy with any of cytosine arabinoside, methotrexate, nitrogen mustard^{15,47}, cyclophosphamide¹⁶ and surgery^{15,39}. In addition, intra thecal therapy was given using cytosine arabinoside or methotrexate or both on different days^{16,39,42,47}. In some instances, treatment never took place or was abandoned due to financial constraints in procurement of chemotherapeutic agents⁴². Complete response rate (defined by complete tumour regression) was less than 50% in all four studies in which it was stated (table 3). Most patients had either partial or non-response. Documented death was highest in the study from Sokoto (85.2%) in which intrathecal chemotherapy was not given. This was followed by an earlier study in Ibadan (77%) in which intrathecal therapy was given only occasionally. Assuming that the non-responders and partial responders eventually died, analysis of the complete response rate and the documented deaths in the present study (with the exclusion of the study from Zaria in which complete response rate was not stated), would yield an estimated overall survival rate that is at best 15-23%. In a recent multicenter funded study involving Kenya, Tanzania and Nigeria, the International Network of Cancer Treatment and Research Protocol 03-06 was used. The event free survival probabilities at 2 years for the two Nigerian centres that participated were 43% at the University College Hospital, Ibadan and 48% at Obafemi Awolowo University Teaching Hospital Complex (17).

Table 3: Treatment outcome for patients with Burkitt Lymphoma

Study	City	Year of Publication	No. of patients treated	No. of patients not treated	Predominant chemotherapy regimen	Complete response % of treated patients	Partial response % of treated patients	Loss to follow up/Abandoned treatment %	Documented deaths %
Aderele&Antia ¹⁵	Ibadan	1979	94	-	CTX Monotherapy	48.8	-	-	77.0
Fasola ⁴⁷	Ibadan	2002	56	10	COAP	22.8	57.9	-	17.5
Taqi ³⁹	Zaria	1987	78	-	COM	Not stated	-	-	33.3
Ibrahim ⁴¹	Sokoto	1998	27	-	COM	Not stated	-	7.4	85.2
Oguonu ¹⁶	Enugu	2002	44	-	COMP	48.0	35.0	59.1	36.0
Kagu ⁴²	Ile-Ife	2004	174	39	COM	29.3	-	77.9	20.7

CTX: cyclophosphamide

COAP: Cyclophosphamide, Vincristine, Cytosine arabinoside, Prednisolone

COM: Cyclophosphamide, Vincristine, Methotrexate

COMP: Cyclophosphamide, Vincristine, Methotrexate, Prednisolone

Discussion

This review has provided an overview of the pattern of occurrence of Burkitt Lymphoma across Nigeria. With the tumour being the most common childhood malignant tumour in 10 out of 12 centres for whom data for all cancers is available, it stands out as the most common childhood cancer nationwide, accounting for between 18.3-65 percent of tumours. Our results also reveal Burkitt Lymphoma to be the most common malignant childhood solid tumour in the country. This study has also shown that Retinoblastoma rather than Burkitt Lymphoma is the most common childhood cancer in Ibadan and Kano, situated in the south western and northwestern geopolitical zones respectively^{12,13} and the most common solid tumour in Lagos, also in the south western zone of the country. Considering studies that were based exclusively on solid tumours, Burkitt Lymphoma remained the commonest solid tumour in most centres with the exception of Jos and Lagos. The placing of Burkitt lymphoma as the third most common tumour in the review by Tanko *et al*²⁸ from Jos needs to be interpreted with caution bearing in mind that Burkitt Lymphoma is mostly diagnosed through cytology of fine needle aspirate and so the Jos study which was based on histology of solid tumours is likely to have an under-representation of Burkitt Lymphoma¹⁷. The predominance of Retinoblastoma among solid tumours in Lagos is similar to the finding in Ibadan which is in the same geopolitical zone. However, the very low frequency of Burkitt lymphoma (2%) in the most recent study from Lagos is a striking feature probably due to the fact that Akinde *et al*²⁹ used only histologically diagnosed cases and so excluded cytologically confirmed cases which might have included cases of Burkitt Lymphoma.

The downward trend in the frequency of Burkitt Lymphoma in Ibadan over time from 51.5% reported by Williams in 1960 to 11.7% reported by Babatunde *et al*¹² in the year 2010 is quite significant. This is similar to findings in Lagos revealed in the present study. Although the exact cause is not clear, it has been attributed to improvement in living conditions and better malaria control measures, given the role of malaria in endemic Burkitt Lymphoma. Knowledge of the factors responsible for this decline would be useful in proffering solutions towards reducing the incidence of the disease. Incidentally, a similar trend was not observed in Enugu. There is a lack of studies on trend of childhood cancer in other parts of Nigeria. Such studies, along with population based incidence studies are necessary nationwide as epidemiological tools to guide the formulation of policy and measures aimed at cancer prevention and control.

The male preponderance of the disease nationwide is in keeping with established findings in Uganda⁴⁸. This review has shown the peak age of Burkitt Lymphoma in Nigeria to be between 5 and 10 years which is similar to the highest age standardized incidence rate observed in 5-9 years in Kenya⁴⁹.

Aderelle and Antia in Ibadan observed that 99 percent of children with Burkitt Lymphoma belonged to the low

socio-economic class. They postulated that frequent infections due to malnutrition to which children from low socio-economic background are prone, makes their immunity too weak to combat the Epstein Barr virus which is associated with Burkitt Lymphoma¹⁵. The present review has shown that between 61.5 and 100 percent of children with Burkitt Lymphoma belong to the low socio-economic class. This suggests a role for low socio-economic status in the occurrence of the disease probably due to associated immunosuppression from malnutrition or poor malaria control from poor living conditions. However, controlled studies are required to establish a firm association between Burkitt Lymphoma and poverty. None-the-less, the difficulties in managing affected children imposed by poverty such as difficulties in investigations, use of suboptimal therapy and abandonment of treatment highlight the important role of poverty in contributing to poor outcome in Nigeria^{42,47}. This calls for government support to treat children with Burkitt lymphoma free of charge. Improvement in the standard of living which is likely to reduce the incidence of the disease is also recommended.

Different epidemiologic forms of Burkitt Lymphoma are characterized by particular clinical features. Whilst the endemic form usually presents with tumours of the facial skeleton as the predominant site, the abdomen is usually the predominant site in the sporadic form of the disease⁽²⁾. The present study has revealed that the jaw and abdomen are the major sites affected in Nigeria, in nearly equal proportions but with a slight predominance of the jaw. However, the age group affected and the geographical location support the belief that the form seen in the country is the endemic form. There is no obvious geographical bias with the pattern as the northern and southern regions of the country each has centres with jaw and abdominal predominant sites. The findings of this study are in keeping with those from other African countries in which the major sites affected are the face and abdomen with slight preponderance of the face as seen Ghana and Uganda^{50,51}. The peak ages ranging from 5-10 years observed in most centres in this review is also in keeping with findings in Kenya and Uganda^{49,51}. The reason why a peak age of 1-5 years was observed in Sagamu is not clear¹⁸.

Data on overall survival and event-free survival from Burkitt Lymphoma in Nigeria are scarce. This study has however revealed a poor outcome of treatment of the tumour in the country due to inability to pay for treatment, frequent abandonment of treatment, use of monotherapy and loss to follow up. In some instances, 7.4 – 77.9 % of patients abandoned treatment and up to 18.3 % could not receive treatment^{41,42}. The chemotherapeutic regimen most frequently used was the COM protocol. Complete response rate in the retrospective reviews was between 22.8 to 48.8 percent. A study on the patterns of treatment failure in Ibadan by Williams *et al*⁵² showed that patients with Partial response and Non-Response were all dead by the 10th observation month. Consequently, the partial and non-responders in this may be assumed to have died. Analysis of the complete

response rate and the documented deaths in the present study (with the exclusion of the study from Zaria in which complete response rate was not stated), would yield an estimated overall survival that is at best 15-23% in the retrospective studies. In the INCTR multicenter study, the EFS probabilities for the Nigerian sites of 43 and 48 percent are better and reflect the improvement that may result from support in funding treatment¹⁷. Our findings are also a sharp contrast to a 5 year survival of 64.7% observed in a South African setting with better laboratory and treatment facilities⁵³.

Conclusion

Burkitt Lymphoma is the most common childhood malignancy in Nigeria but some parts of the country have a

declining trend in its frequency. This may be due to improving socioeconomic status and malaria control. Some areas regions experiencing this decline are observing Retinoblastoma as the predominant childhood cancer. The demographic features are in keeping with those in other parts of the World where endemic Burkitt Lymphoma occurs. Affected families are poor and treatment outcomes bedeviled by financial difficulty in paying for treatment and abandonment of treatment. There is dearth of national data on incidence which calls for establishment of cancer registries to provide the true incidence of the tumour. There is also a need for financial support for treatment of and long term follow up of affected children to facilitate improved outcomes and provide data on survival.

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