bjh review

Optimizing outcomes for children with non-Hodgkin lymphoma in low- and middle-income countries by early correct diagnosis, reducing toxic death and preventing abandonment

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Summary

In high-income countries, more than 90% of children with mature B-cell lymphomas are cured with frontline therapy. However, cure requires prompt and correct diagnosis, careful risk stratification, very intense chemotherapy and meticulous supportive care, together with logistical support for patients who live far from the cancer centre or face financial barriers to receiving care. In low- and middle-income countries (LMIC), cure rates range from 20% to 70% because of lack of diagnosis, misdiagnosis, abandonment of treatment, toxic death and excess relapse with reduced-intensity regimens. Fortunately, a wide range of successful interventions in LMIC have reduced these causes of avoidable treatment failure. Public awareness campaigns have led to societal awareness of childhood cancer; telepathology has improved diagnosis, even in remote areas; subsidized chemotherapy, transportation, housing and food have reduced abandonment; and hand hygiene, nurse training programmes and health system improvements have reduced toxic death. These interventions can be deployed everywhere and at low cost, so are highly scalable. Children and adolescents with Burkitt lymphoma can be cured in all countries by making a timely correct diagnosis, applying protocols adapted to the local context, preventing abandonment of therapy and avoiding toxic death. Reducing these causes of treatment failure is feasible and highly cost-effective everywhere.

Keywords: non-Hodgkin lymphoma, Burkitt lymphoma, B-cell lymphoma, low-income countries, middle-income countries, abandonment, toxic death.

Non-Hodgkin lymphomas (NHL) are some of the most common and curable paediatric cancers in the world, with an estimated 56 000 new diagnoses each year among children 0–19 years old (Steliarova-Foucher *et al*, 2017). In high-income countries (HIC), advances in diagnosis, risk-stratification, optimization of protocols, control of central nervous system disease and supportive care have significantly improved the prognosis of children with NHL over the recent decades (Minard-Colin *et al*, 2015). Data generated by international cooperative groups has enabled tailoring the treatment intensity and clarified the need for various treatment components for specific NHL subtypes, tumour burden and disease extent (Minard-Colin *et al*, 2015). In HIC, intensive chemotherapy regimens can be delivered with toxic death rates of 2% or lower, such that approximately 90% of children with NHL are cured with frontline therapy (Minard-Colin *et al*, 2015). Furthermore, new drugs and immune therapies have improved salvage rates for the 8% who relapse, and some of these survive long-term, even after high-risk relapses (Cairo *et al*, 2018).

Unfortunately, the outlook in areas with limited resources is less optimistic, and 90% of children live in such settings (Fig 1, http://www.worldpopdata.org/map). In low- and middle-income countries (LMIC), avoidable treatment failure results from delayed or even lack of diagnosis, misdiagnosis, abandonment of therapy, excess toxic death and excess relapse due to insufficiently intensive regimens, such that event-free survival (EFS) ranges from 0% to 30% in much of the world (Fig 2) (Hesseling *et al*, 2013; Gross & Biondi, 2016; Gopal & Gross, 2018). Fortunately, each of these causes of avoidable treatment failure can be reduced with proven strategies, as discussed in this review. In most LMIC settings, children experiencing relapses are incurable, so all efforts must be concentrated on achieving cure with frontline therapy. For this review, we focus on the management of mature B-cell lymphomas as these are by far the most common in LMIC and offer the greatest opportunity to reduce treatment failure and save lives. The terms "mature B-cell lymphomas" and "Burkitt lymphoma" are used interchangeably.

Epidemiology

There are major variations in the epidemiology of Burkitt lymphoma, with reported annual incidences ranging from 4

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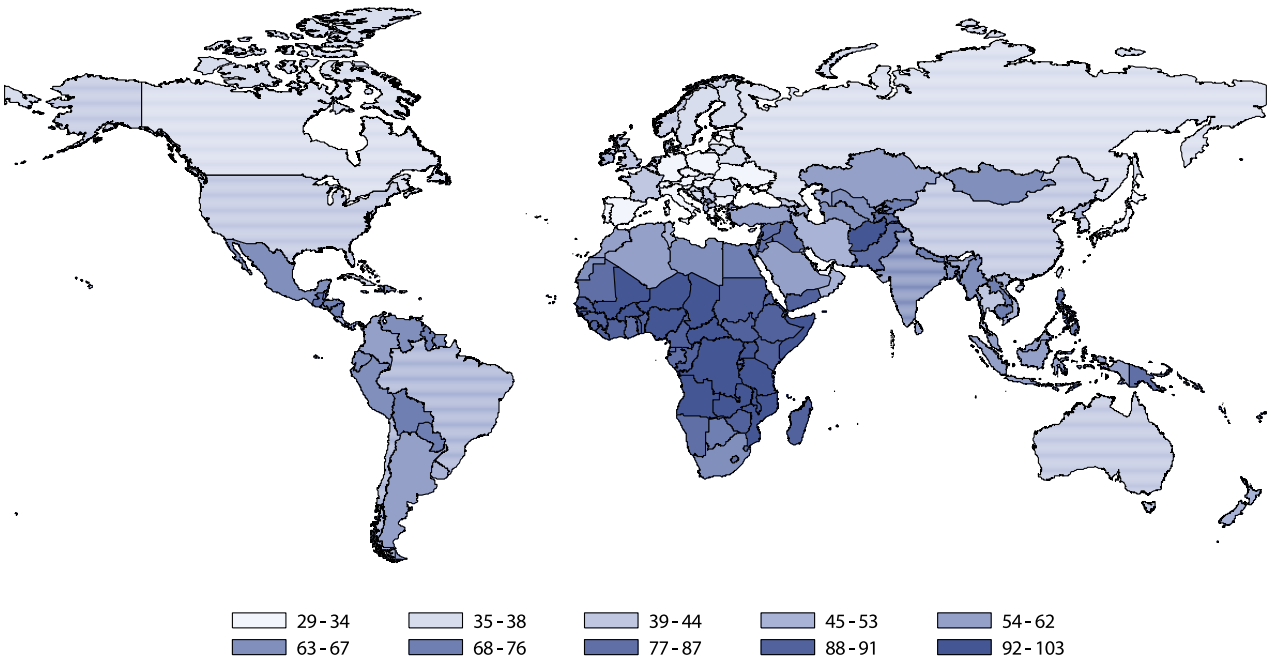

Fig 1. The number of children with cancer per capita is highest in low- and middle-income countries. This map shows the cases of cancer per million people (adults and children) in the population and highlights the relatively high burden of childhood cancer in the poorest countries. Approximately 87% of the world's children live in low- and middle-income countries, where children represent a much higher percentage of the population.

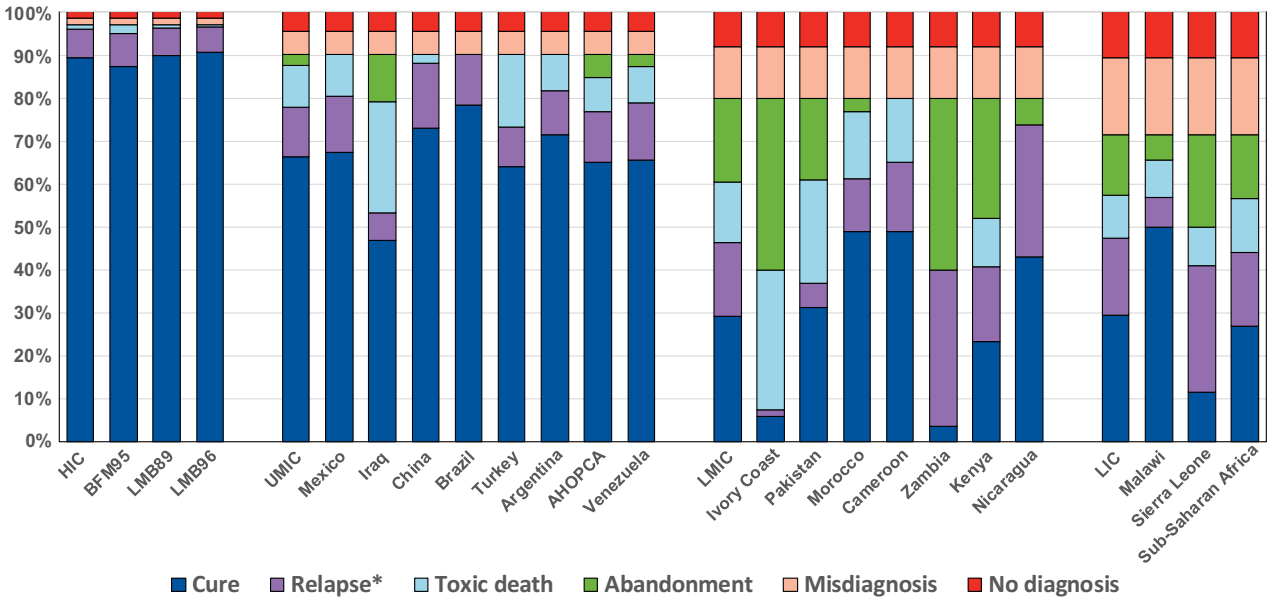

Fig 2. Causes of treatment failure in children with Burkitt lymphoma in selected centres and countries in high- middle- and low-income countries. Causes of treatment failure represent the first adverse event. Many of these causes lead to other subsequent causes of second and third treatment failure, as in the case of patients who abandon treatment then relapse, or those who are misdiagnosed and whose disease then progresses while on inappropriate treatment. Figure used with kind permission of Scott C. Howard, MD, MSc.

to 60 cases per 1 000 000 children depending on the setting, a 15-fold difference based on geographic, ethnic and environmental factors (Stefan & Lutchman, 2014; Steliarova-Foucher *et al*, 2017). Endemic Burkitt lymphoma is highly prevalent in tropical Africa and, despite its presentation as relatively localized disease in many cases, EFS is lower than 50%,

mostly because of comorbid conditions such as malnutrition and infection, low availability of resources for treatment, suboptimal supportive care, and logistical and financial obstacles that lead to treatment abandonment (Traore *et al*, 2011; Marjerrison *et al*, 2012; Gopal & Gross, 2018; Neal *et al*, 2018). However, it is uncertain if it shares the exquisite chemosensitivity shown by sporadic Burkitt lymphoma because there have been no reported results of clinical trials for children with endemic Burkitt lymphoma treated with intensive regimens. There is a close association between Epstein–Barr virus (EBV) infection and endemic Burkitt lymphoma and virtually all patients with endemic Burkitt lymphoma harbour EBV sequences in the tumour genome (Brady *et al*, 2007). Concomitant malaria infection, initially reported many decades ago, has more recently been better characterized (Johnston *et al*, 2014). Also, there is also an increased risk for Burkitt lymphoma in children living in areas where human immunodeficiency virus (HIV) infection is highly prevalent (Mutalima *et al*, 2008), adding additional co-morbidity that could affect outcome. However in a study from Cameroon, the overall prevalence of HIV in children with Burkitt lymphoma was comparable to the general population (Hesseling *et al*, 2018). In middle-income countries (MIC), there is no evidence of increased incidence in Burkitt lymphoma compared to the Western world, and there are no striking differences in clinical presentation compared to higher-income countries, where the most common site of involvement is the abdomen (Ferreira *et al*, 2012; Steliarova-Foucher *et al*, 2017). In fact, differences in sites of presentation in sub-Saharan Africa may be partly due to the use of clinical staging only in many areas with few resources. Patients with abdominal disease who present with an acute abdomen may die without having a diagnosis of lymphoma made, while those with jaw involvement or other head and neck manifestations (e.g. ocular) would rarely die before being diagnosed. The relationship with EBV infection is comparable to that in HIC, but specific molecular features have been reported in some MIC (Liao *et al*, 2018; Uccini *et al*, 2018). There is far less information about the epidemiology and results in other lymphoma subtypes, such as lymphoblastic lymphomas or large cell lymphomas, including anaplastic large cell lymphomas (ALCL), in LMIC (Ceppi *et al*, 2016). In addition, there is relatively little known about certain lymphoma subtypes that are rare in Western countries, such as natural killer (NK) cell cancers, which are much more common in specific regions of LMIC, including East Asia and some Latin American countries (Pillai *et al*, 2016). However, the specific epidemiology, management and outcomes of these other types of NHL will not be addressed here.

Protocol-based care

Children with cancer are typically treated either on a research protocol or according to a published regimen. The "best" regimen has not been determined, but several strategies achieve 90% cure rates in HIC (Reiter *et al*, 1999; Patte *et al*, 2001, 2007; Woessmann *et al*, 2005; Minard-Colin *et al*, 2015; Allemani *et al*, 2018). Regimens for Burkitt lymphoma include several key components, though details for each may differ by study group (Table I). After a careful evaluation of disease extent with imaging studies, bone marrow biopsy, evaluation of the cerebrospinal fluid and the use of lactate dehydrogenase (LDH) as a surrogate for tumour burden, patients are treated with intensive chemotherapy regimens (Reiter *et al*, 1999). Most regimens include a cytoreductive pre-phase, used at the initiation of therapy in order to administer a lower dose of chemotherapy that allows the initial stabilization of the patient and reduces risk of tumour lysis syndrome (TLS) and toxic death (Howard *et al*, 2011). This is usually followed immediately by a 5-day high-dose multi-agent chemotherapy block that aims to deliver the highest intensity treatment to maximize tumour response. In fact, the ability to deliver 2 blocks of intense therapy within 21 days of starting the first block is associated with improved outcomes. This is not surprising considering how rapidly Burkitt lymphoma can grow, such that any treatment gaps provide an opening for disease to progress (Patte *et al*, 2001). The intense block regimens in HIC include high-dose methotrexate, alkylating agents, anthracyclines, vincristine, glucocorticoids and intrathecal methotrexate in doses that induce severe neutropenia, lymphopenia, thrombocytopenia and mucositis, requiring intense supportive care including management of infection, haemorrhage, drug-specific toxicities and nutrition (Patte *et al*, 2001; Howard *et al*, 2005, 2016; Gavidia *et al*, 2012; Israels *et al*, 2013; Bhojwani *et al*, 2014; Gupta *et al*, 2015; Ladas *et al*, 2016). Patients usually develop profound aplasia and opportunistic infections, which necessitate rapid access to intensive life-support. Complete remission is usually obtained after two of these blocks, followed by consolidation therapy. Treatment duration is short, and most patients complete treatment after 4 or 6 blocks given every 2–3 weeks. However, implementing this intensive strategy involves overcoming many challenges at each step, and in many low-income countries (LIC) it is simply not feasible, and lower dose regimens are the only alternative (Depani *et al*, 2015; Buckle *et al*, 2016; Stanley *et al*, 2016). Although such regimens yield EFS lower than the 90% achieved in HIC, they allow a subset of patients to be cured without excess toxicity and are feasible even in the most basic healthcare systems (Howard *et al*, 2007a,b, 2017, 2018).

Management of Burkitt lymphoma in low- and middle-income countries

Many factors contribute to treatment failure in LMIC, including lack of diagnosis, misdiagnosis, abandonment of treatment, toxic death and excess relapse with reduced-intensity regimens (Fig 2). In LIC where endemic Burkitt lymphoma is prevalent, the diagnosis is often based on clinical

Table I. Components of therapy used in different treatment settings.

Protocol	BFM			LMB				SIOP PODC-adapted regimen		
Setting used	High-income countries			High-income countries				Low-income countries		
Risk group	Group A	Group B	Group C	R1	R2	R3	R4	R1	R2	R3
Pre-phase		COP	COP		CPM, DEX	CPM, DEX	CPM, DEX	CPM	CPM	CPM
Induction	COPAD	COPADM x2	COPADM x2	Block A	Block A	Block AA	Block AA	CPM x3	CPM x3	CPM x3
Consolidation	COPAD	CYM x2	CYVE x2	Block B	Block B	Block BB	Block BB		CPM	CPM, VCR, MTX x3
Maintenance		M1	M1, M2, M3, M4		Blocks A, B	Blocks CC, AA, BB	Blocks CC, AA, BB, CC			
CNS control	IT	IT	IT	IT	IT	IT	IT	IT	IT	IT

BFM, Berlin-Frankfurt-Munster; CNS, central nervous system; COP, cyclophosphamide, vincristine, prednisone; COPAD, cyclophosphamide, vincristine, prednisone, doxorubicin; COPADM, cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate; CPM, cyclophosphamide; CYM, cytarabine, methotrexate; CYVE, cytarabine, etoposide; DEX, dexamethasone; IT, intrathecal chemotherapy; LMB, Lymphomes Malins B; MTX, methotrexate; PODC, Paediatric Oncology in Developing Countries; SIOP, Société Internationale d'Oncologie Pédiatrique; VCR, vincristine.

findings and occasionally confirmed by fine needle aspiration cytology because many centres' pathology departments lack access to immunohistochemistry and molecular testing (Hesseling *et al*, 2012; Gopal & Gross, 2018). In LMICs where sporadic Burkitt lymphoma is more prevalent, most patients are biopsied, but when immunohistochemical and molecular characterization of the different lymphoma subtypes is not available, many cases may be classified as a different type of lymphoma, or even as a sarcoma or other cancer type. In these cases, the differential diagnosis of B-precursor lymphoblastic lymphoma from mature B-cell (Burkitt) lymphoma may not be possible, and patients may be inappropriately treated on a generic "NHL" protocol, or worse, on a protocol for a completely different type of cancer. Even in more advanced settings, immunophenotyping may be preferentially available only at select academic or university centres (Wiangnon *et al*, 2011; Tan *et al*, 2013). Some studies from LMIC settings have shown up to 24% discrepancy in samples thought to be Burkitt lymphoma by fine needle aspiration when submitted for second pathology review (Naresh *et al*, 2011). In some settings, as previously described in Sierra Leone, less than 50% of patients with suspected Burkitt lymphoma achieve a verified diagnosis (San Roman *et al*, 2013). Not only is diagnosis problematic in LMIC, but staging and risk stratification can also present difficulties. Lack of imaging modalities may make detection of all sites of disease difficult, and the added cost of performing lumbar puncture and bone marrow biopsy to fully stage each patient may make complete staging economically unfeasible. Tailoring therapy according to LDH values in abdominal lymphomas has been challenging in international cooperative studies due to laboratory differences, but it should be possible to adapt this readily available marker for use in LMIC (Harif *et al*, 2008).

Advanced disease at presentation and resource limitations for the management of initial complications

Toxic death in the first month of therapy can be as high as 10% (Acquatella *et al*, 2004; Gaytan-Morales *et al*, 2018) but it may be up to 30% in higher-risk patients in LMIC (Ahmad *et al*, 2010). Delayed diagnosis contributes to every cause of treatment failure. Patients whose diagnosis is delayed present with more advanced disease and a higher risk of malnutrition, TLS, comorbid infections and great risk for early toxic death (Cervio *et al*, 2012). In some cases, 2–5% of patients died within a few hours of arrival to the hospital before even completing staging evaluation (Moleti *et al*, 2011; Gaytan-Morales *et al*, 2018). Extensive abdominal surgical procedures as well as nutritional deficiencies in some settings may also increase the risk of early toxicity, and chemotherapy dose modifications may be necessary in these cases (Israels *et al*, 2009; Traore *et al*, 2011; Cervio *et al*, 2012; Patte *et al*, 2015; Pribnow *et al*, 2017; Howard *et al*, 2018). Delayed diagnosis with advanced disease not only

increases the risk of toxic death and excess relapse, but also increases the costs and morbidity of treatment, which in turn increases the rate of abandonment of therapy. Indeed, in HIC and some cancer types in LMIC, a delay in diagnosis has not been associated with reduced cure rates (Howard & Wilimas, 2005; Lins *et al*, 2012). However, such studies do not account for the extreme delays in diagnosis that occur in some LIC, where the most severe cases are never diagnosed at all because they succumb to metabolic complications or comorbid illness before a cancer diagnosis can be made (Moleti *et al*, 2011; Gaytan-Morales *et al*, 2018) (Figs 2 and 3). For example, in one study in Pakistan, children with NHL presented with stage 3 disease in 91% of cases and stage 4 disease in the remainder, stages that are associated with much higher morbidity, mortality, and costs of care (Faizan *et al*, 2018).

Intensive chemotherapy is needed to achieve a maximum anti-lymphoma effect for high survival rates, but in settings

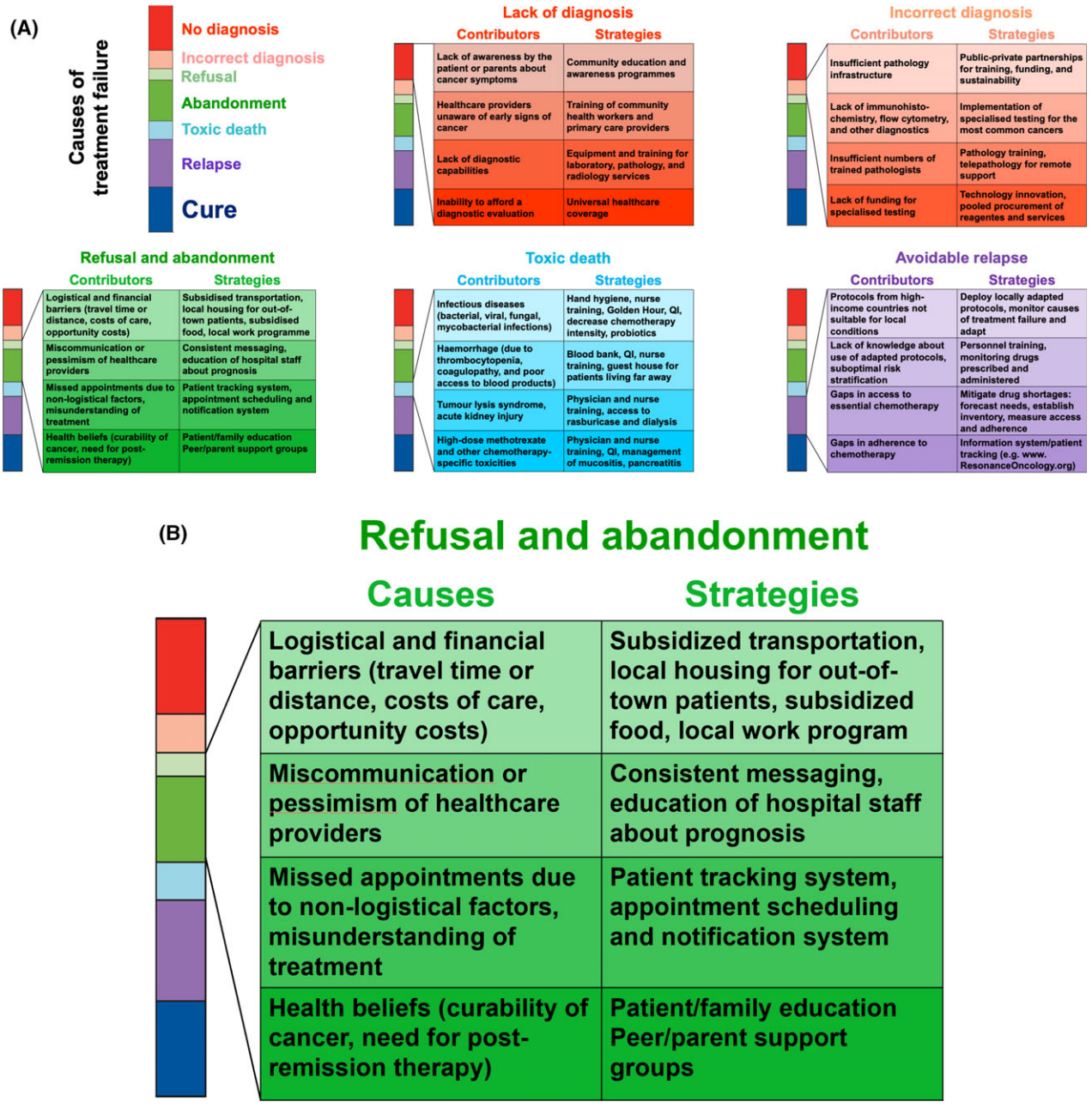

Fig 3. Interventions to address each cause of treatment failure for children with Burkitt lymphoma in low- and middle-income countries. (A) Examples of interventions for all causes of treatment failure. (B) Examples of interventions to prevent refusal and abandonment of therapy. Figure used with kind permission of Scott C. Howard, MD, MSc.

with limited resources, this may not be feasible because of the aforementioned factors. Renal failure at diagnosis is more prevalent in LMIC than in HIC and predicts toxic death in patients treated with a modified Berlin-Frankfurt-Munster (BFM)-based regimen (Cervio *et al*, 2012). Therefore, supportive care during the first few weeks of diagnosis is one of the biggest challenges in LMIC. Use of a low-intensity pre-phase, intensive nutritional support, management of infections and aggressive hydration to prevent TLS effectively reduces early toxic death. Rasburicase improves renal outcomes and reduces the risk for TLS, and is increasingly available in MIC, but rarely in LIC (Cairo *et al*, 2010). Deciding when to start chemotherapy and with which agents is a key decision in this setting. The Asociación de Hemato-Oncología Pediátrica de Centroamérica (AHOPCA) proposed the use of a second pre-phase in patients with tumour lysis or other complications, such as severe infection, a strategy that provides an extra week to stabilize and support the patient prior to intense chemotherapy (Peña-Hernandez *et al*, 2019). Omitting methotrexate from the initial block may be wise, especially in settings where no drug levels are available, when renal failure occurs, or when ascites or a pleural effusion are present, as these can serve as a reservoir for methotrexate and delay its elimination, with potentially fatal results. In addition to the specific therapeutic strategies described above, real-time access to experts has also improved individual patient outcomes. Members of AHOPCA conduct weekly online meetings for case discussion that includes the participating centres, data managers and specialists from St Jude Children′s Research Hospital. Advice is provided on a weekly basis and by email or phone when an urgent patient care issue manifests, support that is especially important during initial patient management (Howard *et al*, 2007b; Peña-Hernandez *et al*, 2019).

Inability to use high-dose chemotherapy regimens and need to modify published effective regimens

Most reports from upper middle-income countries (UMIC), usually regarding patients treated in referral institutions, showed that toxic mortality, especially during remission induction, is higher than in the protocols from major cooperative groups in HIC (Acquatella *et al*, 2004; Klumb *et al*, 2004; Celkan *et al*, 2010). In order to design an effective therapy for Burkitt lymphoma in LMIC, one must weigh the risk of toxic death against that of excess relapse when considering chemotherapy intensification. Improved anti-lymphoma responses have been achieved with higher intensity treatments, which are necessarily associated with an increased risk of toxic mortality in LMIC (Fig 2). There is no proven superiority of any treatment strategy compared to others in less developed countries, and the "best" regimen varies not only by country, but by the specific treatment centre and, most importantly, the individual patient circumstances and disease characteristics. Hence, in MIC, treatment regimens were adapted from the original protocols developed by cooperative groups in HIC, mainly involving reduction in the dose of methotrexate and alkylating agents in order to reduce toxicity. Centres in MIC typically use modified BFM regimens, or in some cases modified French-American-British protocols (Acquatella *et al*, 2004; Klumb *et al*, 2004). The dose of methotrexate in the BFM regimen blocks AA and BB was reduced from 5 g/m^2 in a 24-h infusion, as per the original BFM protocol, to 1–3 g/m^2 in 3- to 24-h infusions. The NHL-BFM-95 study showed that shortening the infusion duration of methotrexate was less toxic than the 24-h infusion, and many LMIC centres now use 4-h infusions routinely to reduce toxic death (Woessmann *et al*, 2005). Rituximab has been added to this regimen by some groups, with encouraging results (Samochatova *et al*, 2014). Rituximab is an attractive agent given its lack of haematopoietic toxicity and its specific mechanism of action against CD20-positive lymphomas. It can be added to lower-intensity chemotherapy regimens to increase their efficacy without adding substantial toxicity (Akbayram *et al*, 2010; Goldman *et al*, 2014). Unfortunately, its high cost makes it unaffordable in many settings. Results from a single centre in Argentina, where the dose of methotrexate in the first induction block was reduced to 1 g/m^2 in a 4-h infusion while adding rituximab (4 weekly doses starting from week 1) for high risk patients demonstrated a decrease in early death and improved survival (Sanchez La Rosa *et al*, 2016). However, it is important to be aware of the high risk of hypogammaglobulinaemia associated with rituximab administration, and the importance of immunoglobulin replacement therapy for deficient patients to reduce the risk of severe infections. Although rituximab was not associated with severe infections in children with Burkitt lymphoma in HIC, it has been associated with higher rates of hypogammaglobulinaemia and toxic death in some LMIC (Chantada, personal communication). In general, high-risk patients should be better managed as in-patients until the second chemotherapy block is given and all these issues are resolved. Careful and consistent infection prevention practices and timely evaluation along with early antibiotic treatment, antifungal therapy and granulocyte colony-stimulating factor support as appropriate are also recommended. In some settings, as adopted by the French-African Paediatiric Oncology Group (GFAOP), intestinal parasite therapy is routinely given prior to the start of lymphoma therapy, with standardized recommendations for antimicrobial management during therapy (Traore *et al*, 2011). Generally, modified (reduced intensity) induction regimens were associated with lower fatal toxicity rates when compared to previous experience in the same centres (Sanchez La Rosa *et al*, 2016). However, shorter methotrexate infusions are not only less toxic, but also less effective in controlling the lymphoma, and this approach to improve patient survival has not been studied in a randomized trial. However, not every centre in MIC uses modified regimens. Reports from selected (specialty) centres in Brazil and China did not show an

increased risk of toxic deaths in their cohorts using unmodified regimens (Klumb *et al*, 2004; Sun *et al*, 2006). However, in these series a higher proportion of lower-risk patients were included, who typically have low rates of toxic death regardless of the setting. Comparative analysis of overall survival results between reports from HIC and LMIC are also limited by the different proportion of high-risk patients in the latter. In most LMIC there is a higher prevalence of advanced disease, as high as 80–90% of patients in some studies compared to 66% in the BFM-95 protocol (Woessmann *et al*, 2005; Ahmad *et al*, 2010; Gaytan-Morales *et al*, 2018). Some results from single institutions in UMIC also document a high prevalence of advanced disease, while others showed a similar pattern to HIC (Klumb *et al*, 2004; Sanchez La Rosa *et al*, 2016). Finally, the BFM-95 intense chemotherapy block CC, containing high-dose cytarabine, steroids and etoposide, is not uniformly used, or is used with lower doses in order to avoid its higher haematopoietic and gastrointestinal toxicity in many MIC (Cervio *et al*, 2012). It is important to maintain a high dose-intensity by compressing the interval between chemotherapy cycles to the shortest possible, especially in high-risk patients, by administering the cycles every 2 weeks. However, this interval between cycles is, in practice, typically longer in LMIC (Chantada *et al*, 1997). Finally, relapse risk can be increased by factors unrelated to the treatment regimen, including drug shortages, lack of adherence and decreased dose-intensity due to comorbid illness, all of which occur more commonly in LMIC (Fig 3) (Cohen *et al*, 2018; Khetrapal Singh & Travis, 2018; Perehudoff *et al*, 2018; Roth *et al*, 2018). Fortunately, many interventions have been documented to decrease each cause of treatment failure (see Fig 3 for examples).

Treatment abandonment

Treatment abandonment, defined as 4 weeks or more of missed appointments during therapy, is a major contributor to treatment failure in less developed countries (Mostert *et al*, 2011). Abandonment of therapy has been reported by most centres in LMIC, but it is quite uncommon in HIC (Gupta *et al*, 2013; Friedrich *et al*, 2015). In some settings, abandonment has been described as the dominant challenge for children with NHL, affecting up to half of the children diagnosed, particularly in rural settings, such as in parts of Zambia (de Boer *et al*, 2009). In Iraq, treatment abandonment was a major contributor to treatment failure in 239 analysed patients with B-cell NHL, despite free treatment, contributing to 25% of treatment failures, with most patients abandoning treatment after pre-phase chemotherapy; the authors postulated that geographic distance from the treatment centre as well as families' misperceptions of cure after initial therapy may have contributed to treatment abandonment (Moleti *et al*, 2011). Interestingly, the authors also noted treatment abandonment disproportionately affecting female patients in their analysis, with 12-month cumulative incidence of abandonment at 22% in females compared to 7% in males ($p < 0{\cdot}001$)(Moleti *et al*, 2011). Yao *et al* (2012) described the prominent challenge of treatment abandonment in Côte d'Ivoire, where nearly half of the children presenting with cancer abandoned treatment shortly after the first admission, resulting in only a 6% cure rate for Burkitt lymphoma. In Sierra Leone, despite shortening the duration of inpatient treatment, providing free treatment with provisions for meals and transportation, treatment abandonment was found to be a persistent challenge in rural areas without an accessible quality referral network (San Roman *et al*, 2013). While often described as a challenge for patients with NHL, several studies have suggested that treatment abandonment may be relatively lower for patients with NHL than those with other diagnoses. In a retrospective cohort analysis in Shanghai, China, abandonment affected 11·5% of 108 patients with lymphoblastic lymphoma, which, the authors noted, was less than the abandonment rates of 13·5–51·3% in patients with acute lymphoblastic leukaemia over the same time period in Shanghai (Gao *et al*, 2014). Of patients with ALCL treated across 6 AHOPCA countries between 2000 and 2013 ($n = 31$), 6·5% abandoned therapy, somewhat lower than the abandonment rate typically experienced with other tumours in the same settings (Ceppi *et al*, 2016). It is possible that abandonment rates in aggressive lymphomas may be lower given the shorter treatment duration (than for leukaemia, for instance) and children are too acutely unwell to be discharged during therapy and thus have less opportunity to abandon treatment. The finding that children with lymphoma may be less likely to abandon treatment upfront, or refuse therapy before starting any treatment, was further noted in a retrospective analysis from Guatemala (Alvarez *et al*, 2017), where 21% of 1789 children abandoned therapy over an 8-year period; a lymphoma diagnosis was associated with a lower likelihood to refuse therapy (Z score $-0{\cdot}686$, $P = 0{\cdot}03$) without an associated lower likelihood in later treatment abandonment. Complex factors can contribute to treatment abandonment, as reported by families in home-based interviews in a study in Kenya, in which NHL patients comprised just over half the study cohort; these factors included advice from others to seek complementary and alternative therapy, and concern over hospital detention due to inability to pay hospital bills (Mostert *et al*, 2014). However, systemic support is paramount, with another retrospective study demonstrating that treatment abandonment was the most common cause of treatment failure for children with NHL in Kenya, affecting 35% of patients, where health insurance access was associated with improved outcomes (Martijn *et al*, 2017). Early preemptive strategies may be helpful. In El Salvador, in addition to free treatment, implementation of a tracking protocol for missed appointments (before patients met criteria for treatment abandonment) successfully prevented treatment abandonment in the majority of patients, including patients with lymphomas, and similar strategies have proven effective in

many settings (Salaverria *et al*, 2015; Suarez *et al*, 2015) (Fig 3).

Limited guidelines and guidance documents

National guidelines for the management of NHL in children are warranted, and ideally would be developed by a defined process of evidence synthesis (including consideration of the local health system context and data from local research), and supported by a sound infrastructure for ongoing monitoring and continuous quality improvement (Thacker *et al*, 2017). Unfortunately, a paucity of local data, lack of infrastructure for clinical research and continuous quality improvement, and lack of funding for and prioritization of local guideline development delay the arrival of locally developed evidence, and recommendations developed in HIC contexts do not consider issues like abandonment and high rates of toxic death. For these reasons, national cancer control plans in resource-limited settings have not traditionally prioritized clinical research, but this is changing rapidly (Weaver *et al*, 2015). For example, using a Delphi consensus methodology, the Colombia Ministry of Health and Social Protection has published a clinical practice guideline for children and adolescents with NHL and Hodgkin lymphoma, using defined methods including GRADE to categorize recommendations (Ministerio de Salud y Protección Social – Colciencias, 2013). Some national efforts have explicitly identified the need for cross-sector engagement, such as recognizing the need for partnership with oral health providers to ensure timely recognition and referral of Burkitt lymphoma in Sierra Leone as part of national essential services (Ministry of Health and Sanitation, Sierra Leone, 2010, San Roman *et al*, 2013). In addition, multi-country collaborative efforts in research and quality improvement have advanced care and improved the local evidence base substantially. The experience of GFAOP and AHOPCA has shown how regional collaborative prospective protocols can be successfully implemented in resource-limited settings, including in sub-Saharan Africa (Traore *et al*, 2011; Peña-Hernandez *et al*, 2019).

Conclusions and future directions

Mature B-cell lymphomas are curable in 90% of cases using conventional high-dose chemotherapy regimens that comprise widely-available inexpensive generic drugs administered according to the patient's risk group. Risk stratification is tailored to disease burden, as practiced in HIC. In LMIC, lack of diagnosis, misdiagnosis, advanced disease, abandonment and toxic death from comorbidities, such as malnutrition and infections, result in cure rates much lower than those in HIC. In LIC, only mild chemotherapy that cures about 50% of children is feasible; whereas in MIC the use of locally adapted high-dose therapies cures 70–80% cure in UMIC and 60–70% in lower-MIC. However, the toxic death rate in these settings still greatly exceeds the 1–3% rates in HIC. Accurate diagnosis, improved supportive care, and the introduction of new less toxic drugs, such as rituximab, and improved supportive care with granulocyte-stimulating growth factors and rasburicase, may improve results worldwide. Tackling treatment abandonment and strengthening the health system to facilitate the completion of treatment in children while avoiding financial or social catastrophe would further improve the results in these highly curable children, especially in LMIC.

Authors contributions

GC, CGL, SCH: Manuscript writing, final approval of the document.

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