Hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia

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ABSTRACT

This article details the 2025 consensus update from the Brazilian Group for Pediatric Bone Marrow Transplantation and the Brazilian Society for Pediatric Oncology regarding hematopoietic stem cell transplantation (HSCT) for pediatric acute lymphoblastic leukemia (ALL). Allogeneic HSCT is the standard treatment for high-risk or relapsed ALL. Key indications include, in first remission, very high-risk patients defined by primary induction failure or positive minimal residual disease (MRD) after consolidation. In second remission, it is indicated for early bone marrow relapse, early isolated extramedullary B-cell relapse, and all T-cell ALL relapses. The consensus recommends myeloablative conditioning as standard, preferring

total body irradiation based regimens for children over 2–3 years old. The preferred donor hierarchy is a matched sibling, followed by a matched unrelated donor, with bone marrow being the preferred cell source. Post-HSCT monitoring of MRD is critical for guiding interventions and identifying relapse. This document serves as an essential, updated guide for clinical decision-making in this field.

Keywords: Precursor Cell Lymphoblastic Leukemia-Lymphoma. Hematopoietic Stem Cell Transplantation. Consensus. Pediatrics.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a highly effective treatment modality for childhood acute lymphoblastic leukemia (ALL). However, given its both acute and long-term complications, specific indications depend on the phase of treatment. At first remission, HSCT is reserved for children with a very high risk of relapse, based on unfavorable clinical and genetic characteristics and poor early response to treatment. In the relapse setting, it is usually indicated for first high-risk relapse and for subsequent relapses of ALL, in which treatment intensification is warranted. In these patients, allogeneic HSCT has an important role by combining radiotherapy, intensive preparative chemotherapy, and the graft-*versus*-leukemia (GvL) effect. Nonetheless, transplant-related morbidity and mortality remain a major challenge.

Currently, immunotherapy has helped improve treatment results in B-cell ALL, being a bridging therapy to transplant, by reducing the toxicity to patients before it, an adjuvant therapy, or even an alternative to HSCT. Advances in chemotherapy regimens have continually been seen concurrently with important improvements in HSCT techniques, donor availability, and ancillary measures. In this scenario, HSCT indications for childhood ALL are a dynamic process that change according to advances in the field of biology, chemotherapy, immunotherapy, and transplant[1,2].

In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation and the Brazilian Society for Pediatric Oncology convened a task force to review and update HSCT indications for childhood ALL. This consensus was revised in 2025 to incorporate new evidence and advances in the field[3].

HEMATOPOIETIC STEM CELL TRANSPLANTATION INDICATIONS FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA IN FIRST REMISSION

HSCT indications for pediatric ALL in first remission are limited and should be guided by the used protocol. Although few molecular abnormalities are associated with poor prognosis, the response to treatment based on minimal residual disease (MRD) is currently the most important prognostic factor for indicating HSCT in first remission. The common HSCT indications for childhood ALL in first remission are:

- Primary induction failure (M2 or M3 marrow at the end of induction), except for children < 6 years old and hyperdiploidy or ETV6-RUNX1[4,5];
- Positive MRD at the end of the consolidation phase (around 12 weeks of treatment), according to the cut-off values set for each treatment regimen used, most commonly above or equal to 10-3 (molecular) or 0.1% (through flow cytometry)[3,6,7];
- ALL diagnosed before 6 months of age are associated with MLL (KMT2A) rearrangement and with other risk factors, such as hyperleukocytosis (> 300,000/mm^3) and non-response to corticosteroids[3];
- Poor-prognosis molecular abnormalities, such as t(17;19), are indications for HSCT in children in first remission when TCF3-HLF is present, regardless of MRD status in modern protocols HSCT[1,8].

HSCT indications for pediatric ALL in second remission are[3]:

- Children with early bone marrow relapses of ALL (less than 36 months of remission or in the first six months after the end of treatment);

- In late bone marrow or extramedullary relapse of B-cell ALL, chemotherapy and HSCT exhibit similar results, so chemotherapy should be preferred, except in cases with persisting MRD positivity;
- Early isolated extramedullary relapses of B-cell ALL (< 18 months of first remission);
- For children with T-cell ALL, regardless of whether there is early or late relapse or if there is medullary or extramedullary relapse[9].

In third remission, despite a survival benefit with HSCT, results are much worse. Patients without morphological remission do not benefit from transplantation[3] (Table 1).

Table 1. Hematopoietic stem cell transplantation indications for pediatric patients: Brazilian Group for Pediatric Bone Marrow Transplantation consensus recommendations for acute lymphoblastic leukemia.

Disease	Allogeneic				Autologus
	Familiar		Unrelated		
	MSD	HAPLO	MUD	MMUD	
ALL 1 CR very high risk	Yes	Yes	Yes	Yes	No
2 CR high risk	Yes	Yes	Yes	Yes	No
3 CR	Yes	Yes	Yes	Yes	No

ALL: acute lymphoblastic leukemia; CR: complete remission; MSD: matched sibling donor; HAPLO: familiar haploidentical donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor. Source: Elaborated by the authors.

WHICH IS THE BEST DONOR?

Human leukocyte antigen (HLA) matched related donors remain the most appropriate choice in terms of engraftment and earlier immune reconstitution, with less severe infectious complications, in the allogeneic HSCT setting for childhood ALL[10]. However, overall survival and non-relapse mortality (NRM) have been improving over the years in unrelated donor (URD) transplants with an HLA match > 9/10, with similar results[11,12]. The post-transplant cyclophosphamide (PTCy) platform has also shown favorable results in children without an MRD or URD[12]. The FORUM study proposed the following hierarchy for choosing a suitable donor: HLA-matched sibling donor (MSD) > HLA-matched URD (MUD) > mismatched unrelated donor (MMUD) or familiar haploidentical donor (HAPLO)[13]. In cases in which a mismatched donor is selected, screening for anti-HLA and donor-specific antibodies is recommended to reduce the risk of graft failure[11].

WHICH IS THE BEST STEM-CELL SOURCE?

For children, bone marrow is the preferred stem cell source in comparison to peripheral blood stem cells, given the higher incidence of chronic graft-*versus*-host disease (GvHD) and transplant-related mortality (TRM) with the latter[10,14,15]. The use of umbilical cord blood as stem cell source has shown worse TRM in Brazil[14,16], the main limiting factor for its use being the low stem cell count in each umbilical cord blood unit, HLA disparity permission in the selection, and center experience[14].

WHICH IS THE BEST CONDITIONING REGIMEN?

Myeloablative conditioning (MAC) regimens remain the standard of care for HSCT in childhood ALL. Reduced intensity conditioning (RIC) has not been shown to be of benefit in the treatment of ALL due to increased treatment failure (Fig. 1)[17]. Even though most children with ALL undergo HSCT with MAC regimens including total body irradiation (TBI)[18,19], recent studies are trying different chemotherapy-based protocols to effectively replace TBI, particularly in children under 2 years old. However, a retrospective study comparing TBI *versus* cemotherapy showed that TBI-based conditioning has better outcomes (overall survival and NRM) and is the standard of care in the treatment of ALL in children older than 2–3[20]. The only prospective trial randomizing

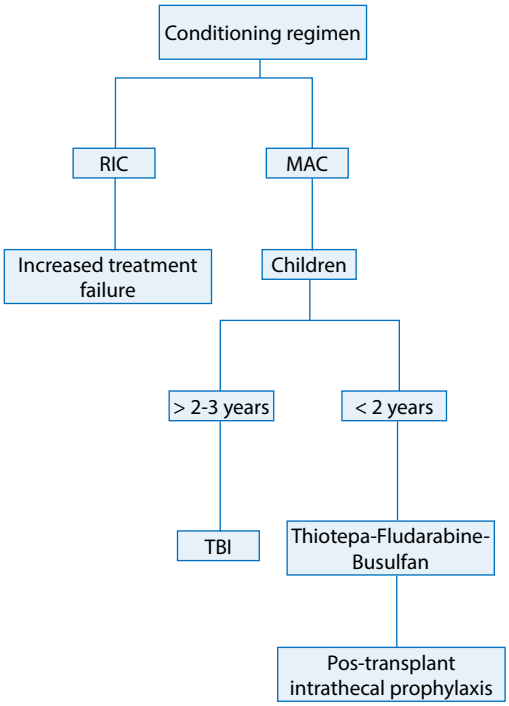

Figure1. Flowchart of conditioning choice for Pediatric Acute Lymphoblastic Leukemia.

children older than 4 years old to conditioning therapy with TBI—etoposide or thiotepa—fludarabine—busulfan (or treosulfan) demonstrated superiority of TBI in terms of lower relapse rate, TRM, and improved overall survival (91 *versus* 75%, $p < 0.0001$)[13]:

- Central nervous system (CNS) boost irradiation[13,20–23]: Patients without a history of CNS involvement during remission do not receive additional cranial irradiation. Patients with CNS involvement at any time of the disease may require boost irradiation. The international FORUM protocol also recommends post-transplant intrathecal prophylaxis whenever TBI is not part of the conditioning therapy. They suggest four weekly triple intrathecal administrations starting around D+60 if the patient is already stable and has greater than 50,000 platelets/mm^3;
- Testicular irradiation: Additional local irradiation is not given in cases with primary testicular lesions or in cases with combined testicular relapses. Due to the accelerated irradiation, the biological effectiveness of TBI corresponds to approximately 15 Gy conventional dose. Also, the myeloablative therapy by chemotherapy should facilitate sufficient control of testicular leukemic infiltrations. However, previous testicular irradiation is not a contraindication against TBI[13];
- Conditioning regimen[10,13,24,25]: TBI has historically been used in combination with high doses of cyclophosphamide (120 mg/kg), with favorable overall survival and event-free survival results, yet with considerable short- and long-term toxicity. Over the past few years, the association of TBI with etoposide has yielded somewhat better results with respect to overall survival, disease-free survival, and TRM[13] (Table 2).

WHAT IS THE BEST GRAFT-*VERSUS*-HOST DISEASE PROPHYLAXIS REGIMEN IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA?

This summary outlines the different prophylactic regimens used to prevent GvHD in HSCT. The specific regimen depends on the donor type, with the details provided in Table 3.

Notably, methotrexate (MTX) is primarily used for unrelated or mismatched donor transplants, not for HLA-matched sibling transplants.

Table 2. Suggested hematopoietic stem cell transplantation conditioning for pediatric acute lymphoblastic leukemia.

MSD	TBI (12Gy) D-3 to D-1 + CY (120 mg/kg) D-7 to D-4 or TBI (12Gy) D-6 to D-4 VP16 (60 mg/kg) D-3
MUD	TBI (total 8Gy) D-7 to D-4 + FLU (total 150 mg/m^2, D = 8 to D-4) + CY (total 120 mg/kg D-3 and D-2) + ATG (7.5 mg/kg total dose over 3 days) or TBI (total 12Gy) D-8 to D-5 + VP16 (60 mg/kg) D-4 + ATG (total 7.5 mg/kg total dose) D-3 to D-1
Haploidentical	TBI (total 12Gy) D-4 to D-2 + FLU (total 90 mg/m^2) D-7 to D-5 + PTCY (total 100 mg/kg) D+3 and D+4 or TBI (total 12Gy) D-6 to D-4 + VP (60 mg/kg) D-3 + PTCY (total 100 mg/kg) D+3 and D+4
For children < 48 months old	
MSD	BU (AUC 18,000–20,000 mM × min) D-7 to D-4 + FLU (150 mg/m^2) D-7 to D-3 + TT (10 mg/kg) D-2
MUD	BU (AUC 18,000–20,000 mM × min) D-7 to D-4 + FLU (150 mg/m^2) D-7 to D-3 + TT (10 mg/kg) D-2 + ATG (7.5 mg/kg) D-3 to D-1
Haploidentical	BU (AUC 18,000–20,000 mM × min) D-7 to D-4 + FLU (150 mg/m^2) D-7 to D-3 + TT (10 mg/kg) D-2 + PTCY (100 mg/kg) D+3 and D+4

MSD: matched sibling donor; MUD: matched unrelated donor; TBI: total body irradiation; Cy: cyclophosphamide; VP16: etoposide; FLU: fludarabine; ATG: thymoglobulin; BU: busulfan; TT: thiotepa. Source: Elaborated by the authors.

Table 3. Graft-*versus*-host disease prophylaxis regimen in childhood acute lymphoblastic leukemia.

MSD	CSP 2 mg/kg or TAC 0.05 mg/kg in two divided IV doses—started on D-1 (SL CSP: 100–200 mcg/L or TAC: 5–15 ng/mL
MUD	Short-term MTX (D+1, D+3, D+6)* + CSP or TAC
HAPLO	PTCy 50 mg/kg (D+3 and D+4)** + CSP or TAC + MMF 15 mg/kg/dose q8h; max 2g/day — started on D+5
UCB	Combination of CSP or TAC + MMF 15 mg/kg/dose q8h; max 2 g/day

*MTX is used at doses of 10 mg/m^2, all of which with leucovorin rescue after 24 h; **coupled with mesna (100–160% of the Cy dose); MSD: matched sibling donor; MUD: matched unrelated donor; HAPLO: haploidentical; UCB: umbilical coord blod; CSP: cyclosporin; TAC: tacrolimus; SL: serum levels; MTX: methotrexate; PTCy: post-transplant cyclophosphamide; MMF: mycophenolate mofetil. Source: Elaborated by the authors.

For pediatric patients receiving unrelated donor HCT, anti-thymocyte globulin (ATG) is often used, but its overall benefit remains unclear. While a study found that lower ATG doses can reduce infections while maintaining similar GvHD and relapse rates, different ATG formulations make definitive conclusions difficult[3,13,26–28].

CLINICAL SIGNIFICANCE OF MINIMAL RESIDUAL DISEASE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE LYMPHOBLASTIC LEUKEMIA

MRD before allogeneic HSCT is a strong predictor of relapse and survival in pediatric ALL. Higher pre-HSCT MRD levels correlate with increased relapse risk and lower survival rates:

- MRD ≥ 0.1% is linked to high relapse risk (CIR 40–67%), while MRD 0.01–0.1% has a lower impact[29–31];
- MRD-negative patients have the best outcomes (CIR 5–20%), with NGS-based detection showing even lower relapse rates[32].

Notably, data from the FORUM study suggest that pre-HCT MRD positivity may not translate into poorer outcomes, especially in patients who received TBI, suggesting that this approach may mitigate the negative impact of MRD positivity[13].

While pre-HSCT MRD is an important prognostic marker, post-HSCT MRD monitoring is even more predictive. High post-HSCT MRD levels strongly indicate recurrence, whereas early low-level positivity does not always lead to relapse[33]. However, the risk increases significantly beyond 100 days post-transplant[30,32,34].

Regular MRD monitoring is essential, as it changes over time. Patients with later MRD positivity face higher relapse risks. Acute GvHD appears protective, reducing relapse rates regardless of MRD status[32].

NGS-MRD can be more sensitive than multiflow Cytometry MFC-MRD in detecting relapse risk, but it requires further validation[35].

In addition to MRD assessment, chimerism is a valuable tool for detecting impending relapse, providing complementary prognostic information. Studies show that increasing mixed chimerism strongly correlates with relapse risk, while decreasing mixed chimerism is linked to better outcomes, reinforcing its role in dynamic risk stratification. Furthermore, increasing mixed chimerism can be detected several months before relapse[36–38].

MRD should be assessed following the standard schedule outlined in Table 4, with chimerism monitored accordingly.

Systematic MRD monitoring is essential for risk stratification and therapeutic decision-making in HCT.

Table 4. Recommended minimal residual disease and chimerism monitoring schedule.

Timepoint	Assessment frequency
Pre-HSCT	At least one month before transplant (ideally 14 days before)
Post-HSCT	Minimum: Days +30, +60, +90, +180, +270, +360
High-risk cases	Monthly bone marrow evaluations in the first year post-HSCT

HSCT: hematopoietic stem cell transplantation. Source: Elaborated by the authors.

MINIMAL RESIDUAL DISEASE-GUIDED INTERVENTIONS

Post-HSCT MRD evaluation is critical for identifying high-risk patients and guiding interventions aimed at either inducing a GvL effect or directly targeting residual leukemia cells.

GvL-based approaches:

- Immunosuppression withdrawal: it should be discontinued as soon as MRD+ or mixed chimerism is detected. Taper until discontinuation within one week;
- Donor lymphocyte infusion (DLI): recommended in the FORUM protocol as an immediate intervention, administered one week after immunosuppression withdrawal[10,13];
- Recommended dose: $1x10^6$ CD3+/kg, which can also be used in haploidentical transplants if no active GvHD is present. DLI can be repeated after one month if mixed chimerism or MRD+ persists in the absence of GvHD.

IMMUNOTHERAPY STRATEGIES FOR MINIMAL RESIDUAL DISEASE POSITIVITY

Blinatumomab, inotuzumab, and even CAR-T cell therapy can be considered for patients with persistent MRD after HSCT.

Preventive strategies for relapse are described in detail in the relapse prophylaxis chapter.

SPECIAL CONSIDERATIONS

Adolescents and young adults

HSCT plays a critical role in the management of adolescents and young adults with ALL. Most high-risk features influencing transplant eligibility include positive MRD after induction and/or at the end of consolidation, as well as adverse cytogenetic profiles, such as hypodiploidy and recently identified high-risk mutations like *KMT2A* rearrangement[39]. The Children's Oncology Group enrolls patients aged 1 to 30 in most protocols; thus, one of the current discussions is the definition of the age cut-off for young adults. In patients with B-precursor ALL, HSCT has also shown advantages in cases featuring focal deletions of the *IKZF1* gene[40]. It is essential to recognize that HSCT outcomes in adolescents and young adults patients are generally poorer than in pediatric populations, primarily due to increased treatment-related mortality associated with chronic GvHD[41].

Both blinatumomab and inotuzumab may be utilized to achieve MRD negativity in first-line therapy prior to transplantation in patients diagnosed with B-ALL[42]. For patients with Philadelphia chromosome-positive ALL, the treatment landscape is rapidly evolving; therefore, transplantation should be carefully discussed and considered for those with MRD-positive disease and high-risk features, such as *IKZF1* deletions. For patients with T-ALL, fewer drugs have been incorporated, so allogeneic HSCT (allo-HSCT) should be considered in cases of residual disease, high-risk features, and relapse, using similar criteria as in children and adolescents to indicate transplantation. Allo-HSCT remains an important therapeutic option for adult and young adult patients with high-risk ALL, especially in cases of inadequate MRD response[39–41]. Regimens involving TBI are traditionally recommended for young patients with ALL, but concerns about long-term toxicity, including the increased risk of chronic GVHD, persist[43,46–48]. The use of post-transplant cyclophosphamide (PTCy) is increasingly in treatment protocols for both related and unrelated allogeneic transplants. Its post-transplant use is particularly relevant concerning the prevention of GvHD, and in the context of the adult and young adult subgroup, it becomes an interesting strategy, with even greater relevance in unrelated donors with disparity.

The choice of conditioning regimen in HSCT for ALL in the adult and young adult group should balance TBI-based regimens with chemotherapy options like thiotepa, considering the MRD response and the risk of complications such as chronic GvHD. The use of PTCy may be an effective strategy, and the decision should take into account the patient's risk profile and the characteristics of the conditioning regimen[48,49].

INFANT ACUTE LYMPHOBLASTIC LEUKEMIA

ALL in infants, particularly those with the KMT2A (MLL) gene rearrangement (KMT2A-r) that accounts for 80% of cases, has been a challenging disease with reported event-free survival rates of 50%. The last few years have seen the emergence of novel therapies that are both more effective and less toxic than conventional chemotherapy[39,40].

High-risk patients are candidates for HSCT, with risk classification varying according to the treatment protocol. In most cases, it includes factors such as age below 1, slow response to initial therapy assessed by MRD, and poor prognostic genetic abnormalities, such as hypodiploidy, KMT2A rearrangement, and TP53 mutations[39].

Deciding upon the best choice of conditioning and weighing the possible lifelong consequences of sequelae against the risk of relapse is a very challenging decision[41].

The FORUM protocol provided a platform for safe allo-HSCT in young children with high-risk ALL and achieved low NRM rates using the conditioning regimen Bu/Flu/Thio or Treo/Flu/Thio for children under 4 years old. A historical comparison of the three-year event-free survival and overall survival rates was low (55 and 68%) compared to historical cohorts of patients aged 2 to 4 receiving TBI/Eto (83 and 91%), as reported in the ALL-SCT BFM2003 trial and the ALL-SCT BFM International trial[41].

Our suggestion is to use TBI/VP for children > 2 years old, and chemotherapy-based protocol for those above 2 years old at the time of transplant (see conditioning regimens).

OVERVIEW OF TOTAL BODY IRRADIATION

Conditioning with TBI plays a crucial role in HCT for childhood ALL[3,13].

Advantages of TBI for conditioning of ALL[10,11,24,43]:

- Antileukemic effect: TBI is highly effective in eradicating leukemic cells, especially in sanctuaries such as the CNS and the testicles;
- Uniform penetration: In contrast to chemotherapy, TBI has a uniform effect on all tissues, including those that are poorly reached by chemotherapy;
- Synergism with chemotherapy: TBI is often combined with chemotherapy, such as with Cy or VP-16, to enhance the efficacy of the conditioning regimen.

Second hematopoietic stem cell transplantation

In developed countries, children who relapse after an allo-HSCT for ALL often have access to CAR-T therapy, significantly improving outcomes. However, in Brazil, access is restricted, making a second HSCT the most viable curative option. Despite its potential for cure, the second HSCT carries significant toxicity; therefore, relapse prevention is crucial through MRD and chimerism monitoring, early immunosuppression withdrawal, and maintenance therapy.

Survival rates range from 20 to 40%, with better outcomes observed in patients with a B-cell phenotype, late relapse (defined as occurring more than six months after transplant), remission at transplant, or isolated extramedullary relapse[43,44].

Donor selection is critical. While reusing the same donor may reduce GvHD, switching may enhance GvL, though survival benefits remain unclear[45]. HLA loss occurs in 10–30% of post-HSCT relapses, making leukemic cells resistant to donor immunity. Testing is essential, as switching to a donor targeting remaining HLA antigens is recommended. In these cases, DLI are ineffective[46]. Unfortunately, HLA loss testing is limited in Brazil. As testing requires > 20% blasts, early relapse assessment is crucial. Donor single antigen (DSA) screening is also important, as DSAs increase the risk of graft failure, particularly in haploidentical or mismatched transplants.

Conditioning regimens must balance efficacy and toxicity. MAC is preferred for longer remission and no toxicity, using TBI (if not previously given) or busulfan-based regimens, often combined with thiotepa for better CNS penetration[47,48]. RIC is suitable for patients with prior toxicity or early relapse, incorporating fludarabine, busulfan, melphalan, or low-dose TBI[49,50]. Since most children maintain good clinical status and many have already received TBI, the conditioning regimen with busulfan, fludarabine, and thiotepa is a suggested alternative.

Children undergoing second HCT face a high risk of relapsing, making post-transplant maintenance therapy advisable, particularly as CAR-T is challenging to access for B-ALL and unavailable for T-ALL. Close MRD and chimerism monitoring enable early interventions. Given these challenges, a tailored approach, including optimal donor selection, conditioning, and relapse prevention, is crucial to improving survival.

CONCLUSION

Allo-HSCT remains the treatment of choice for children with high-risk or relapsed ALL. Outcomes with URD transplants have progressively improved, now approaching those achieved with MSD. The introduction of PTCy in haploidentical transplantation has further expanded donor availability by overcoming HLA barriers. However, several factors must be carefully considered to optimize outcomes, including the advantages and limitations of TBI-based conditioning regimens, the choice of GvHD prophylaxis, and the need for long-term follow-up of this population.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Daudt LE, Correa ACR, Zanette A, de Macedo AV, Breviglieri CNM, Kuwahara C, de Castro Jr CG, Domingues LSS, Klinger P, Ikoma M, Lins MM,

Guimarães R, Fernandes Jr V, Bouzas LF and Seber A. **Conception and design:** Daudt LE, Correa ACR, Zanette A, de Macedo AV, Breviglieri CNM, Kuwahara C, de Castro Jr CG, Domingues LSS, Klinger P, Ikoma M, Lins MM, Guimarães R, Fernandes Jr V, Bouzas LF and Seber A. **Analysis and interpretation of data:** Daudt LE, Correa ACR, Zanette A, de Macedo AV, Breviglieri CNM, Kuwahara C, de Castro Jr CG, Domingues LSS, Klinger P, Ikoma M, Lins MM, Guimarães R, Fernandes Jr V, Bouzas LF and Seber A. **Technical procedures:** Daudt LE, Correa ACR, Zanette A, de Macedo AV, Breviglieri CNM, Kuwahara C, de Castro Jr CG, Domingues LSS, Klinger P, Ikoma M, Lins MM, Guimarães R, Fernandes Jr V, Bouzas LF and Seber A. **Statistics analysis:** Daudt LE, Correa ACR, Zanette A, de Macedo AV, Breviglieri CNM, Kuwahara C, de Castro Jr CG, Domingues LSS, Klinger P, Ikoma M, Lins MM, Guimarães R, Fernandes Jr V, Bouzas LF and Seber A. **Manuscript writing:** Daudt LE, Correa ACR, Zanette A, de Macedo AV, Breviglieri CNM, Kuwahara C, de Castro Jr CG, Domingues LSS, Klinger P, Ikoma M, Lins MM, Guimarães R, Fernandes Jr V, Bouzas LF and Seber A. **Final approval:** Daudt LE.

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