Acute Lymphoblastic Leukaemia
PI ALL-1 Protocol

(PI ALL-1, will continue to be used in some countries-eg Samoa.
(PI ALL-2 does not replace PI ALL-1,
but is for those countries resourced for a more intensive regimen-eg Fiji and Tonga)

NCCN Pacific Island Working Group Clinical Members

Scott Macfarlane
Peter Bradbeer
Jane Skeen
Rob Corbett
Siobhan Cross
Radhika Sandilya

TREATMENT OUTLINE

Prephase (phase 0, 1 week)

IT MTX, Prednisone.

Induction (phase 1, 5 weeks)

IT MTX, Prednisone, Vincristine, Pegaspargase

CNS prophylaxis/Consolidation (phase 2, 6 weeks)

IT MTX, Vincristine, Cyclophosphamide, ARA-C

Continuous Maintenance (phase 3, 96 weeks)

IT MTX, Vincristine, Dexamethasone, 6-Mercaptopurine, Methotrexate

1. IT MTX for first year of therapy only

Abbreviations:

VCR = vincristine; PDN = prednisone; Peg-asp = Pegaspargase;
Cyclo = cyclophosphamide; Ara-C = cytarabine; MTX = methotrexate;
ITMTX = intrathecal methotrexate; 6MP = 6-mercaptopurine;
DEX = dexamethasone;

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1.0 AIMS

Primary

1.1 To increase the proportion of children with acute lymphoblastic leukaemia (ALL) who are cured.

Secondary

1.2 To assess the ability of Pacific Island health systems to deliver chemotherapy according to an adapted protocol.

1.3 To assess the ability of Pacific Island health systems to provide supportive care guided by protocol and shared care consultation from NZ centres.

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2.0 RATIONALE FOR STUDY DESIGN

Children and young people in the Pacific have not enjoyed the survival of their peers in developed health systems. This has been the result of a number of factors including late or non diagnosis, treatment toxicity on protocols considered standard in developed health systems and treatment abandonment due to expense and family dislocation. This protocol has been drawn from strategies used by NZ and Australian paediatricians to treat children with ALL in the past, at a time when the ability to treat and support children with malignant disease was at an early stage of development.

The protocol should be able to be delivered in its entirety in Fiji. Eligible patients in Samoa and Tonga will receive prephase in their base hospital and good responders will be referred to NZ for Induction and CNS prophylaxis/consolidation. All patients will be repatriated for ongoing maintenance therapy (or palliative care if not achieving remission)

3.0 PATIENT ELIGIBILITY

3.1 Newly diagnosed children with ALL aged between 1 and 18 years of age (inclusive) without B-cell ALL (FAB L3) are eligible.

3.2 Patients who have blast counts >1 x109/L in peripheral blood after the 7 day prednisone (and ITMTX) prophase come off protocol and receive symptomatic care.

3.3 Patients who are not in remission on the Day 35 BMA come off protocol and receive symptomatic/palliative care.

4.0 EXCLUSIONS

4.1 Patients with B-cell ALL [FAB L3]

4.2 Patients aged ≤ 1 year or ≥ 18 years at diagnosis

4.3 Patients with WBC >200x 10^9/L are not eligible

4.4 Patients with CNS disease (CNS blasts > 5 x 10^6/L) are not eligible

4.5 Patients with Down syndrome.

5.0 INITIAL EVALUATION

5.1 Complete history including family history

5.2 Complete physical examination including careful documentation of size of lymph nodes, spleen and liver size, presence of extra-medullary involvement
Measure height and weight and calculate surface area

5.3 Chest X-ray

5.4 Full blood and platelet count

5.5 Bone marrow aspirate (BMA)/trephine

5.51 For morphology and cytochemistry

5.6 CSF examination

5.61 For cell count

5.62 For cytospin

5.7 Biochemistry
(liverfunction/urea,electrolytes,creatinine,urate,calcium,phosphate), cultures, mantoux, virology (Hepatitis B) etc according to clinical circumstances and individual institution's requirements. Note a negative mantoux does not exclude Tb.

6.0 REGISTRATION

6.1 Upon diagnosis all patients with ALL will be recorded on the unit registry.

7.0 TREATMENT

All eligible patients receive identical therapy. CNS preventative therapy will vary according to age. Total length of therapy is 102 weeks (2 years) from documentation of remission (see 7.5).

7.1 Induction therapy should not commence until appropriate supportive care has been given. This includes correction of anaemia and thrombocytopenia, treatment of infection, appropriate hydration, allopurinol and correction of electrolyte disorders.
A suggested routine is - allopurinol 300 mg/m^2/day in 3 divided doses - Hydration at 3000mL/m^2/day (125mL/m^2/hour) with 4% Dextrose and 1/5 N Saline, initially potassium free. Individual institutions may have different concentrations dextrose saline (3.5% dextrose/1/3 N saline)

7.2 For patients in Samoa and Tonga, initiate proceedings for referral to NZ at day 8 should the patient be a good responder to prednisone prephase.

7.3 PREPHASE- 1 WEEK
All eligible patients will begin prednisone prephase after confirmation of diagnosis on bone marrow aspiration and following lumbar puncture and administration of age appropriate dose of intrathecal methotrexate.

7.31 Prednisone 40 mg/m2 orally in 2 divided doses Days – 7 to 22 then taper

7.311 Hyperglycaemia - no modification will be made and insulin therapy will be used (see 7.421)

7.312 Hypertension - reduce dose by 50% and consider sodium restriction and anti-hypertensives

7.313 Pancreatitis - if severe, cease

7.32 Intrathecal methotrexate

7.321 Methotrexate will be administered according to an age-related formula:

Age	1-2 years	2-3 years	>3 years
Dose	8mg	10mg	12mg

Perform lumbar puncture and if CSF flowing freely collect 4-5 mls and send CSF for cytospin and a smaller volume for culture.

If CSF blood stained this makes analysis difficult due to blood contamination. May need to resite needle.

Inject IT methotrexate as a slow push. There should be no resistance.

Peripheral blood count on day 8 determines ongoing treatment. Patients with differential lymphoblast counts less than 1x 10^9/L are regarded as good responders and will go on to induction therapy. Patients who have persisting elevations in peripheral blood blast counts are regarded as unfavourable prognosis patients who are unlikely to be cured without intensive therapy which this protocol does not offer.

In Fiji, good responders will proceed to induction. In Samoa and Tonga, good responders will be sent to New Zealand.

7.4 INDUCTION THERAPY - 5 WEEKS

During induction therapy no dose will be delayed **solely** because of myelosuppression.

7.41 Vincristine 1.5mg/m^2 (maximum dose 2mg) IV push on Days 1, 8, 15 and 22.

7.411 Seizures secondary to vincristine - withhold one dose then reinstitute (on anticonvulsant therapy).

7.412 Severe foot drop, paralytic ileus - withhold dose and resume at 1mg/m^2. When symptoms abate, escalate to full dose as tolerated.

7.413 Jaw pain - treat with analgesics and do not modify vincristine dose.

7.414 Defer if abnormal liver function is present (AST >10x upper limit of normal or bilirubin >30 μmol/L). Resume when liver function is returning to normal.

7.42 Prednisone 40 mg/m^2/day orally in 2 divided doses on days 1-21 and then tapered over 7 days as per the following:-

20mg/m^2/day for 2 days, 10mg/m^2/day for 2 days, 5mg/m^2/day for 2 days, 2.5mg/m^2/day for one day.

7.421 Hyperglycaemia - no modification will be made and insulin therapy will be used.

7.422 Hypertension - reduce dose by 50% and consider sodium restriction and anti-hypertensives.

7.423 Pancreatitis - if severe, cease.

7.43 With the discontinuation of production worldwide of **E coli (LEUNASE) L-asparaginase– this will be replaced by Pegaspargase 2500 U/m^2 IV x 1 dose on Day 4, 5 or 6 (not on a weekend) with a premedication- refer APPENDIX A1.4**

7.431 Premedication: Loratadine 1 hour prior to Pegaspargase dose

Loratadine dose: 1-2 years = 2.5mg

2-12 years and under 30kg = 5mg
2-12 years and over 30kg = 10mg
12-18 years =10mg

7.44 Intrathecal Methotrexate Days -7 and 15

Age	1-2 years	2-3 years	> 3 years
Dose	8 mg	10mg	12mg

7.441 Omit if renal failure present and substitute cytarabine (Ara-C).

7.442 Omit if Grade 3 or 4 stomatitis (ulcers and liquid diet only or alimentation not possible) and substitute Ara-C.

7.443 Intrathecal dose of Ara-C

Age	1-2 years	2-3 years	> 3 years
Dose	20 mg	24 mg	30mg

7.444 Patients with a CSF white cell count of $<5 \times 10^6$/L but with unequivocal lymphoblasts on cytospin will receive additional intrathecal methotrexate on days 8 and 22.

7.5 Documentation of Remission

A bone marrow aspirate will be performed on Day 36, which then becomes Day 1 of the next phase of therapy. If marrow is M1 proceed with next phase. Remission is defined as a normocellular marrow with <5% blasts present. Any patient who fails to achieve remission on day 36 will be off protocol.

7.51 Therapy is given for 102 weeks (2 years) from documentation of remission.

8.0 CNS PREVENTATIVE - CONSOLIDATION THERAPY 6 WEEKS

CNS preventative - consolidation therapy commences provided the patient is in remission and the absolute neutrophil count is $>0.5 \times 10^9$/L and the platelet count is $>80 \times 10^9$/L. Once begun the first 14 days of chemotherapy will be given without interruption, unless life threatening complications are present (this will almost always only be sepsis). The second phase due on Day 22 should only be commenced if the absolute neutrophil count is $>0.5 \times 10^9$/L and the platelet count $>80 \times 10^9$/L. Once commenced this pulse should only be interrupted for life threatening complications.

Commence *Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole (see appendix A1.1).

8.1 CNS PREVENTATIVE THERAPY

8.11 Intrathecal Methotrexate Days 1, 8, 15 and 22

All patients receive intrathecal methotrexate in age related doses (see 7.32). Send CSF for cytospin.

8.2 CONSOLIDATION

Consolidation commences provided the patient is in remission (see 7.5) and the absolute neutrophil count is $>0.5 \times 10^9$/L and the platelet count $>80 \times 10^9$/L. Once begun, the first 14 days of chemotherapy will be given without interruption, unless life threatening complications are present (this will almost always only be sepsis).

8.21 Vincristine 1.5 mg/m^2 (maximum dose 2 mg) IV on Days 1 and 8 and on Days 22 and 29 (see 7.41 to 7.414).

8.211 The third dose of vincristine due on Day 22 (and cyclophosphamide and Ara-C, see 8.523) should only be given if the nadir has been

passed and the absolute neutrophil count is >0.5 x10^9/L and the platelet count >80 x10^9/L.

8.22 Cyclophosphamide 1000 mg/m^2 IV on Days 1 and 22 (see appendix A1.2).

8.221 Gross haematuria - consider using mesna with subsequent doses.

8.222 Microscopic haematuria - add frusemide to IV fluid regimen and continue IV fluids for at least 24 hours.

8.223 Remember that the second dose of cyclophosphamide commencing on Day 22 (and the vincristine {see 8.511} and the Ara-C {see 8.531}) should only be given if the nadir has been passed and the absolute neutrophil count is >0.5 x10^9/L and the platelet count >80 x10^9/L.

8.23 Ara-C 75 mg/m^2/day IV or subcutaneously (dependant on concentration of Ara-C- if 100mg/5mls for IV) on Days 1-4, 8-11, and 22-25, 29-32.

8.231 the dose due on Day 22 at the time of the second dose of cyclophosphamide and vincristine (see 8.523) should only be given if the nadir has been passed and the absolute neutrophil count is >0.5 x10^9/L and the platelet count >80 x10^9/L.

8.232 Withhold if bilirubin >25 umol/L or transaminases >2.5x upper limit of normal (grade 3 hepatotoxicity).

8.233 Do not modify for rash.

9.0 CONTINUATION THERAPY - 96 weeks

This therapy continues provided complete continuous remission is maintained until 2 years of therapy, from the time of documentation of remission, (see 7.5) has been given.

Need to ensure a regular supply of medication and need to emphasise the importance of compliance. Aim is to avoid where possible interruptions in therapy. Dose reduction may be needed due to cytopaenia but uninterrupted therapy at a lower tolerable dose better than interrupted chemotherapy at protocol doses. If neutrophil counts are consistently high despite increasing doses, check lymphocyte count. If > 1.5 suspect non-compliance as an explanation.

CONTINUATION

Continuation therapy only commences if the absolute neutrophil count is >1.0 $x10^9$/L and the platelet count >100 $x10^9$/L. Blood counts should be done at least once every 28 days (ie with each VCR) or more frequently if dose adjustment of 6MP is necessary (see 9.32 to 9.35). Liver function tests (LFT's) are recommended every 8 weeks or more frequently if clinically indicated. **Continue** trimethoprim-sulfamethoxazole prophylaxis.

9.1 Vincristine 1.5mg/m^2 IV every 28 days (see 7.41 to 7.414).

9.11 Vincristine and the 5 day pulse of dexamethasone are to be given together every 28 days irrespective of blood count (see 9.21).

9.2 Dexamethasone 6mg/m^2/day orally for 5 days every 28 days in 2 divided doses

9.21 Dexamethasone and the IV push of vincristine are to be given together every 28 days irrespective of blood counts (see 9.11).

9.3 6-mercaptopurine 50mg/m^2/day continuously

9.31 6MP is given at the same time each day. If vomiting occurs within 2 hours the full dose should be repeated. The aim is to give 350 mg/m^2/week as shown in the following table:

MERCAPTOPURINE 50mg/m^2/day		
surface area	dose per week (tabs)	daily dose
0.47 – 0.53	3.5	half a tablet daily on 7 days
0.54 – 0.6	4	half a tablet daily on 6 days and one tablet on day 7
0.61 – 0.67	4.5	half a tablet daily on 5 days and one tablet daily on 2 days
0.68 – 0.74	5	half a tablet daily on 4 days and one tablet daily on 3 days
0.75 – 0.82	5.5	half a tablet daily on 3 days and one tablet daily on 4 days
0.83 – 0.89	6	half a tablet daily on 2 days and one tablet daily on 5 days
0.9 – 0.96	6.5	half a tablet on one day and one tablet daily on 6 days
0.97 – 1.03	7	one tablet daily on 7 days
1.04 – 1.1	7.5	one tablet daily on 6 days and one and a half tablets on day 7
1.11 – 1.17	8	one tablet daily on 5 days and one and a half tablets daily on 2 days
1.18 – 1.24	8.5	one tablet daily on 4 days and one and a half tablets daily on 3 days
1.25 – 1.32	9	one tablet daily on 3 days and one and a half tablets daily on 4 days
1.33 – 1.39	9.5	one tablet daily on 2 days and one and a half tablets daily on 5 days
1.4 – 1.46	10	one tablet daily on one day and one and a half tablets daily on 6 days
1.47 – 1.53	10.5	one and a half tablets daily on 7 days
1.54 – 1.6	11	one and a half tablets daily on 6 days and two tablets on day 7
1.61 – 1.67	11.5	one and a half tablets daily on 5 days and two tablets daily on 2 days
1.68 – 1.74	12	one and a half tablets daily on 4 days and two tablets daily on 3 days
1.75 – 1.82	12.5	one and a half tablets daily on 3 days and two tablets daily on 4 days
1.83 – 1.89	13	one and a half tablets daily on 2 days and two tablets daily on 5 days
1.9 – 1.96	13.5	one and a half tablets on one day and two tablets daily on 6 days
1.97 – 2.03	14	two tablets daily on 7 days
2.04 – 2.1	14.5	two tablets daily on 6 days and two and a half tablets daily on day 7

9.32 An FBC is performed every 28 days prior to each vincristine and dexamethasone pulse. If the neutrophil count drops to between 0.5-1.0x10^9/L and/or the platelet count to 50-100 x10^9/L then both 6-mercaptopurine and methotrexate should be reduced by 25%. The count should then be repeated at weekly intervals.

9.33 When counts recover to neutrophils >1.0x10^9/L and platelets >100x10^9/L then resume therapy at standard dose.

9.34 If the neutrophil count is <0.5x10^9/L and/or the platelet count <50x10^9/L then oral 6-mercaptopurine and methotrexate are ceased. Upon recovery to neutrophils >1.0 and platelets >100 therapy is resumed at 50% of standard doses and increased to 75% and 100% as tolerated. (This will usually be at 2 week intervals).

9.35 For patients who maintain counts of neutrophils >1.0x10^9/L **and** platelets >100 x10^9/L for a minimum of 2 weeks the dose of 6-mercaptopurine should be increased to 75 mg/m^2/day. If this dose is tolerated then the dose should be increased to 100 mg/m^2. The methotrexate dose remains constant at 20 mg/m^2/week.

9.36 If prolonged cytopaenia > 3weeks, recommend stopping weekend cotrimoxazole. If still cytopaenic at 4-6 weeks recommend BMA to exclude relapse. Unhelpful often to do an earlier marrow as hypocellular marrows are difficult to interpret, so best to wait.

9.4 **Methotrexate 20 mg/m^2 orally weekly** Oral methotrexate is given once a week, for convenience at the same time as that day's dose of 6-mercaptopurine as per following table:

METHOTREXATE 20mg/m^2/week			
surface area	Dose per week (mg)	number of tablets	
		2.5mg	10mg
0.4	7.5	3	-
0.41 – 0.46	8.75	3 ½	-
0.47 – 0.53	10	-	1
0.54 – 0.59	11.25	½	1
0.6 – 0.65	12.5	1	1
0.66 – 0.71	13.75	1 ½	1
0.72 – 0.78	15	2	1
0.79 – 0.84	16.25	2 ½	1
0.85 – 0.9	17.5	3	1
0.91 – 0.96	18.75	3 ½	1
0.97 – 1.03	20	-	2
1.04 – 1.09	21.25	½	2
1.1 – 1.15	22.5	1	2
1.16 – 1.21	23.75	1 ½	2
1.22 – 1.28	25	2	2
1.29 – 1.34	26.25	2 ½	2
1.35 – 1.4	27.5	3	2
1.41 – 1.46	28.75	3 ½	2
1.47 – 1.53	30	-	3
1.54 – 1.59	31.25	½	3
1.6 – 1.65	32.5	1	3
1.66 – 1.71	33.75	1 ½	3
1.72 – 1.78	35	2	3
1.79 – 1.84	36.25	2 ½	3
1.85 – 1.9	37.5	3	3
1.91 – 1.96	38.75	3 ½	3
1.97 – 2.03	40	-	4
2.04 – 2.09	41.25	½	4
2.1	42.5	1	4

9.41 Grade 2-4 nephrotoxicity (creatinine >2.6x upper limit of normal) - omit until toxicity resolved (Grade 0, creatinine <1.25x upper limit of normal).

9.42 Grade 3-4 hepatotoxicity - omit until Grade 0-2 toxicity then resume at half dose. Escalate dose at 2 weekly intervals, provided Grade 3-4 toxicity does not recur.

	Grade 1	Grade 2	Grade 3	Grade 4
ALT	>3x ULN	3-5 x ULN	5-20 x ULN	>20 x ULN
AST	>3x ULN	3-5 x ULN	5-20 x ULN	>20 x ULN

9.43 Grade 2 stomatitis (erythema, ulcer, can eat solids) of >3 days duration, decrease dose by 30%. Grade 3-4 stomatitis - withhold until resolved and resume dose at 50%.

9.44 The dose of oral methotrexate due on the week intrathecal methotrexate is given, but is reduced by the amount of the intrathecal dose (see 9.52).

9.45 Dose guidelines for methotrexate follow those listed in 9.32 to 9.35.

9.5 **Intrathecal methotrexate in age related doses** (see 7.32 to 7.321). Send CSF for cytospin.

9.51 Intrathecal methotrexate is given every 8 weeks during continuation therapy until completion of 12 months of treatment from time of remission (see 9.54).

9.52 The dose of oral methotrexate at this time is reduced by the amount of the intrathecal dose (see 9.44).

9.53 Intrathecal methotrexate is given every 8 weeks but should be deferred if the absolute neutrophil count is $<0.5 \times 10^9$/L and/or platelet count is $<50 \times 10^9$/L.

9.54 **IT MTX is ceased after the first year of therapy** (see 9.51).

9.6 Continuation therapy is given until 2 years of treatment from the time of documentation of remission has been given (see 7.0, 9.0).

9.7 Record details of therapy (when IV vincristine and IT methotrexate/oral 6MP and MTX given) on the flow sheets (accessed with prescription on SSH guideline/Pacific protocols). This will facilitate protocol review and audit for producing outcome data.

9.8 Non- compliance. If families non-compliant and cease therapy, and the child subsequently relapses, symptomatic treatment will be required. (see 10.5).

10.0 COMPLETION OF THERAPY

Following completion of 2 years of therapy documentation of remission with a bone marrow aspirate and diagnostic lumbar puncture is no longer considered standard practice and is not recommended.

10.1 Patients will need to be followed at set intervals to document progress including continuing remission and late effects of treatment (if any- expected to be minimal). A full blood count should be performed at the first visit off treatment and if normal no further blood tests unless clinically indicated.

10.2 When off treatment 6 months, provided well and in remission, re-immunise as per recommended schedule- refer chapter on infections.

10.3 Relapse

10.31 Bone marrow relapse - >25% lymphoblasts irrespective of the proportion of lymphocytes. If marrow rating is M_2 (5-25% lymphoblasts) the marrow should be repeated in 4 weeks time.

10.32 CNS relapse - >5 white cells $x10^6$/L plus cytocentrifuge examination confirming morphologically unequivocal lymphoblasts.

10.33 Testicular relapse - unilateral or bilateral testicular enlargement. Biopsy is required to confirm diagnosis.

10.34 All patients should have both bone marrow examination and CSF examination performed at the time of relapse.

10.4 Death.

10.5 Parents' or patient's refusal to follow assigned therapeutic regimen. Follow up data will still be required for these patients.

11.0 SAMPLE PARENT INFORMATION SHEET

Parent Information Sheet

Pacific Acute Lymphoblastic leukaemia Protocol

Your child has acute lymphoblastic leukaemia (ALL). This is a disorder of unknown cause where there is unrestrained growth of abnormal lymphoblasts (primitive white blood cells) in the bone marrow. Because the production of these abnormal cells is uncontrolled the bone marrow is unable to produce usual numbers of normal red blood cells, white blood cells and platelets. Once produced in the bone marrow, the leukaemic cells (lymphoblasts) have the potential to spread to any part of the body.

ALL is now a curable disease in some children. Research has lead to the identification of certain features of ALL which are present at diagnosis. Such features are referred to as prognostic features. Depending on the prognostic features present at diagnosis, children with ALL can be divided into subgroups, with some groups having a good chance of cure, and some groups having a poor chance of cure. Children who have a good chance for cure will be offered treatment on this protocol. It is impossible to predict whether an individual child will be cured. This information has been designed to help you understand the principles of treatment of ALL and the way it will be given to your child. Remember there are differences between the features present at diagnosis in children with ALL. It is important to remember this fact when discussing and comparing your child's diagnosis, treatment, and progress with other families.

Your consultant will keep you fully informed. Should you have any questions regarding your child's illness or treatment please ask the staff caring for your child. As leukaemia is an illness which has an impact on the whole family, it is important everybody understands how the treatment is given, and why it is given in the way it is. The family is an equally important part of the treatment team as are the doctors, nurses, social workers, pharmacists, chaplains etc.

Your child will receive standard antileukaemic treatment according to this protocol

The therapy on this protocol is divided into a number of phases. It continues over two years provided the child remains leukaemia free. Your consultant will discuss all aspects of the treatment with you and provide you with a copy of the treatment your child is scheduled to receive. Initial treatment, called prednisone prephase will be given to all patients. A good response to this treatment will allow your child to continue with treatment. The next phase is remission induction. This phase, lasting five weeks is aimed at making the leukaemia disappear. This is achieved in most patients. The ongoing treatment is aimed at preventing return of the leukaemia (relapse). More than 50% of patients should remain free of leukaemia at the end of

treatment. The next phase of treatment, called CNS preventative/consolidation therapy lasts six weeks. CNS preventative therapy provides treatment directly to the central nervous system (CNS) by injecting drugs directly into the spinal fluid by means of a lumbar puncture. This is referred to as intrathecal therapy. Consolidation therapy is also given at this time.
Continuation therapy follows consolidation. This phase lasts until the end of treatment. It consists of oral and intravenous therapy. Intrathecal therapy is given every eight weeks during continuation therapy until one year of treatment is completed.

The following is a list of drugs your child may be given. The treatment may need to be modified according to your child's tolerance and side effects he/she experiences. If you have questions please ask a staff member. The most common side effects are listed below:-

Vincristine (VCR) – Given intravenously
- Skin burn if the drug leaks from the vein
- Constipation
- Jaw pain
- Convulsions
- Hair loss
- Leg pain
- Low blood counts

Prednisone (PDN) – given orally
- Weight gain
- Water retention
- Irritability
- High blood pressure
- Diabetes
- Decreased ability to fight infection

Dexamethasone (DEX) – given orally
- As for prednisone

Pegaspargase –given by intravenous injection, with a premedication given 1 hour prior.
- Allergic reactions
- High blood sugar and high lipids
- Inflammation of the pancreas
- Liver function abnormalities
- Loss of appetite and lethargy

Methotrexate (MTX) – given intrathecally
- Irritation of the membranes around the brain and spine
- Convulsions
- Headache, backache, fever
- Learning difficulties

Methotrexate (MTX) – given orally or intravenously

Nausea and vomiting
Mouth ulcers
Rash
Liver or kidney function abnormalities
Learning difficulties
Low blood counts

Cytarabine (Ara-C) – given by injection under the skin or intravenously
Nausea and vomiting
Low blood counts
Rash and fever

Cytarabine (Ara-C) – given intrathecally
As for Methotrexate given intrathecally

Cyclophosphamide – given intravenously
Nausea and vomiting
Hair loss
Low blood counts
Bladder irritation
Infertility (very rare)
Second cancers (very rare)

6-Mercaptopurine (6MP) – given orally
Low blood counts
Liver function abnormalities
Anorexia

Your consultant will discuss in detail all phases of the treatment protocol your child will receive, including the side effects and possible complications associated with treatment. You need to be informed of the range of possible side effects. Some children will experience few of the side effects while other children may experience many. Whilst your child will follow the protocol, the exact treatment received will be adjusted to allow for individual tolerance. Again this may seem to mean differences in treatment of the same disease during discussion with other families.

We hope this information is helpful to you and will enable you, your child and family to understand and cope with the necessary treatment which we hope will achieve cure.

12.0 TREATMENT SCHEMA

PI ALL-1 protocol

Prephase/Induction							6 weeks
Days	**-7**	**1**	**8**	**15**	**22**	**29**	**36/1**
	M_{it}			M_{it}			
		V	V	V	V		

Peg-asp

PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPppppppp

BMA BMA

Key	Drug	Dose	Route	Days
M_{it}	Methotrexate	Age related (max 12mg)	IT	-7 and 15
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,8,15,22
Peg-asp	Pegaspargase	2500 U/m^2 x1 dose	IV	4,5 or 6 (not on a weekend)
P	Prednisone	40mg/m^2/day	O	-7 to 21
p	Prednisone	tapering dose	O	22-29

BMA Bone marrow aspirate on days -7, 36

CNS Preventative/Consolidation Therapy							6 weeks
Days	**1**	**8**	**15**	**22**	**29**	**36**	**43/1**
	M_{it}	M_{it}	M_{it}	M_{it}			
	V	V		V	V		
	C			C			
	AAAA	**AAAA**		**AAAA**	**AAAA**		

Key	Drug	Dose	Route	Days
M_{it}	Methotrexate	Age related (max 12mg)	IT	1,8,15,22
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,8,22,29
C	Cyclophosphamide	1000 mg/m^2	IV infuse x1hr	1/22
A	Ara-C	75 mg/m^2/day	SC/IV	1-4,8-11,22-25,29-32

Pneumocystis prophylaxis See Appendix A1.1

Continuation Therapy									96 weeks
Days	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57/1**
	M_{it}								M_{it}
	V				V				V
	DDDDD				**DDDDD**				**DDDDDD**
	M	M	M	M	M	M	M	M	M

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Key	Drug	Dose	Route	Days
M_{it}	Methotrexate	Age related (max 12mg)	IT	1 ***First year only***
V	Vincristine	1.5 mg/m^2 (max 2mg)	IV	1,29
D	Dexamethasone	6 mg/m^2/day	O	1-5,29-33
6	6-mercaptopurine	50 mg/m^2/day	O	1-56
M	Methotrexate	20 mg/m^2/week	O	1,8,15 etc

APPENDIX 1

A1.1 *Pneumocystis* prophylaxis

All patients should receive prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ). This should commence with the consolidation phase of chemotherapy (section 8). TMP-SMZ then continues throughout therapy.
The dose is 5 mg/kg/day of TMP given in a divided dose (bd) for 2 days/week.

Cotrimoxazole Liquid (240mg/mL) Dose - Twice Daily on Saturday and Sunday			
Weight of Patient (kg)	**Suspension 240mg/5ml**	**Dose of combined cotrimoxazole (mg)**	**Dose of trimethoprim component (mg)**
3 to 3.9	**1mL**	48	8
4 to 5.5	**1.5mL**	72	12
5.6 to 7	**2mL**	96	16
7.1 to 8.8	**2.5mL**	120	20
8.9 to 10.4	**3mL**	144	24
10.5 to 12	**3.5mL**	168	28
12.1 to 13.6	**4mL**	192	32
13.7 to 15.2	**4.5mL**	216	36
15.3 to 16.8	**5mL**	240	40
16.9 to 18.4	**5.5mL**	264	44
18.5 to 20	**6mL**	288	48
20.1 to 21.6	**6.5mL**	312	52
21.7 to 23.2	**7mL**	336	56
23.3 to 24.8	**7.5mL**	360	60
24.9 to 26.4	**8mL**	384	64
26.5 to 28	**8.5mL**	408	68
28.1 to 29.6	**9mL**	432	72
29.7 to 31.2	**9.5mL**	456	76
31.3 to 32.8	**10mL**	480	80
Cotrimoxazole tablet (480mg) Dose - Twice Daily on Saturday and Sunday			
Weight of Patient (kg)	**480mg tablet**	**Dose of combined cotrimoxazole (mg)**	**Dose of trimethoprim component (mg)**
15 to 22.5	**½ tablet**	240	40

Cotrimoxazole Liquid (240mg/mL) Dose - Twice Daily on Saturday and Sunday			
22.6 to 37.5	**1 tablet**	480	80
37.6 to 52.5	**1 ½ tablets**	720	120
> 52.6	**2 tablets**	960	160

A1.2 Cyclophosphamide consolidation therapy (section 8.52, 10.21 and 14.21)

i) Prehydrate with dextrose/saline (0.18% saline + 4% dextrose or 0.3% saline and 3.5% dextrose) + 20mmol/L potassium chloride at 125mL/m^2/hr for 2 hours.

ii) $5HT_3$ antagonist (ondansetron) if available, otherwise metoclopramide for nausea and vomiting.

iii) Give cyclophosphamide 1000mg/m^2 in 125mL/m^2 of above fluid over 1 hour OR add cyclophosphamide 1000 mg/m^2 to 50 mL of N saline or 5% dextrose and infuse over 1 hour as a side line together with hydration fluid at 125mL/m^2/hour.

iv) When cyclophosphamide is completed continue hydration fluid rate at 125mL/m2/hour for 4 hours post cyclophosphamide.

A1.3 Parental handling of oral medication (6MP/MTX)

i. Wash hands before and after handling tablets.
ii. For halving tablets either use a pill cutter or a clean knife-dedicated for this use only.
iii. Gloves are not necessary.
iv. Store tablets at room temperature.

A 1.4 Asparaginase

High risk of anaphylactoid reaction and respiratory arrest with asparaginase administration

This can occur immediately during the intravenous infusion and later with the intramuscular administration. The risk of hypersensitivity increases with each dose. Reactions like shortness of breath, difficulty breathing, rash and redness on the injection site may occur following administration

Always have adrenaline, oxygen, and IV steroids available at time of administration

Ensure medical staff members are present at the time of administration and for the period of **2 hours** post the administration of asparaginase. It is recommended that the patient remain within the hospital setting for at least **2 hours** post administration for monitoring

Pre-administration

The child and family should be made aware of all procedures and tests required prior to, during and post administration of asparaginase.
Ensure the child and their family are aware of the signs and symptoms of asparaginase reactions and are able to inform staff members when appropriate. For potential adverse reactions of asparaginase, refer to the potential side effects section of this of this guideline.

Check that the child has had asparaginase prescribed. Ensure the following:

- Full blood count (FBC) - ensure that the platelets are above $30x10^9$ /L for intramuscular administration. Transfuse platelets if required. It is recommended to administer IM Pegasparagase at least an hour post platelet transfusion.
- Liver function tests (LFTs) - ensure that LFTs have been reviewed by the Paediatrician at the commencement of the treatment protocol
- Urine - prior to administration of asparaginase, perform a urinalysis. If the urine is positive for glucose, notify the Paediatrician
- Prepare the "Emergency Medication Sheet" **(refer Appendix A1.5)**
- Emergency equipment is available and functioning at the patient's bedside.
- Medical staff members are aware and available on the ward during administration and for a minimum of one hour after the administration of the asparaginase.
- **Premedication with Loratadine for any asparaginase product – 1hour prior**

Loratadine dose: 1-2 years = 2.5mg
2-12 years and under 30kg = 5mg
2-12 years and over 30kg = 10mg
12-18 years =10mg

- **If <u>prior reaction</u>** and planned for <u>re-challenge</u> add Hydrocortisone 1 mg/kg IV (max 100 mg)

Safe preparation and administration of asparaginase

Preparation/reconstitution/administration

Asparaginase is available in two different formulations (see below).

Formulation	Brand name	Vial size	Route of administration
Pegaspargase (Pegylated E. Coli asparaginase)	Oncaspar®	3,750 units per 5 mL (750 units/mL)	Intramuscular or Intravenous
Crisantaspase (Erwinia asparaginase)	Erwinase®	10,000 units	Intramuscular or Intravenous

- With the discontinuation of production worldwide of **E coli (LEUNASE) L-asparaginase– this will be replaced by Pegaspargase 2500 U/m^2 IV x 1 dose on Day 4 with a premedication.**
- Pegaspargase is the most commonly used formulation in current leukaemia protocols.
- Pegaspargase does not require further dilution prior to administration
- Although asparaginase is not a cytotoxic agent, it should be handled with cytotoxic precautions. Gloves and a gown should be worn, and the equipment used in administration should be disposed of appropriately

Pegaspargase preparation for intravenous administration

- Withdraw the required dose and dilute in 100 mL of sodium chloride 0.9% or glucose 5%. Infusion over 1 - 2 hours

Patient care following administration and discharge planning

Post administration, ensure that:

- the child and family are informed of the common expected side effects of asparaginase that can occur both short and long term e.g. loss of appetite, skin rash, allergic reaction, localised skin reaction, polyuria, hyperglycaemia
- the child and family are provided with a copy of medication handout that supports the education on potential side effects

- the child and family are advised to contact their treating oncology centre or their shared care hospital, if they suffer any side effects which require intervention
- the process of administration is documented in the patient's clinical record and the chemotherapy/medication chart is signed appropriately
- As asparaginase can cause an allergic reaction leading to anaphylaxis, the child must remain within the administration setting (with access to medical staff members, adrenaline, oxygen, and intravenous steroids) for at least 2 hours post the completion of asparaginase administration. At this point, the nurse or doctor should assess the injection site for any allergic reaction and intervene and document as appropriate prior to discharge.

Adverse effects

Hypersensitivity reactions are the most common dose limiting toxicity. These are reported in up to two thirds of patients receiving intensive schedules.

Allergy or anaphylaxis.

Pain and non-allergic inflammation are not an indication to withhold Pegasparagase

Hypersensitivity can occur within 30 - 60 minutes of receiving asparaginase and is more common with intravenous administration. Pegasparagase is the least immunogenic formulation. The risk of a hypersensitivity reactions increases after several doses have been administered.

The risk of developing a hypersensitivity reaction is greatest when:

- Patients are not receiving steroids
- More than a month has elapsed since the last dose of asparaginase
- The drug is given by intravenous administration

Resuscitation facilities should be close at hand.

Other adverse effects:

- **Hyperglycaemia** - insulin therapy will be used as required.
- **Pancreatitis** - if symptomatic and hyperamylasaemia is present (> 2.6x upper limit of normal).
- **Bleeding** (not due to thrombocytopenia) or thrombosis.
- **Coagulation abnormalities** - haemorrhagic and thrombotic Stroke syndrome or cerebral thrombosis or haemorrhage.
- Abnormal liver function tests
- Hyperlipidaemia
- Hyperuricaemia

- Hyperglycaemia
- CNS side effects: drowsiness, confusion, headache, hallucinations and personality changes

A1.5 Emergency Medication Sheet- Anaphylaxis

1st Line Therapies	**Actual dose**	**Dose Calculation**
Adrenaline (1:1000) IM Anaphylaxis Dose		0.01mL/kg (max 0.5mL)
Oxygen via hudson or non-rebreather	6-8 L/min	6-8 L/min
0.9% Sodium Chloride *Fluid Bolus*		10-20mL/kg (max 2L)
2nd Line Therapies (symptomatic, non lifesaving therapies)		
Adrenaline (1:1000) Nebulised dilute to a minimum of 4 mL		0.5mL/kg (max 6mL)
Hydrocortisone (100mg in 2mL)		4mg/kg (max 100mg)
Loratadine (oral)	5mg	5mg