Great Ormond Street Hospital for Children NHS Foundation Trust

University College London Hospitals NHS Foundation Trust

The Royal Marsden NHS Foundation Trust

Paediatric Haematology & Oncology:

Supportive Care Protocols

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LONDON CANCER NORTH AND EAST

LONDON CANCER ALLIANCE West and South LCA

Jump to Contents Summary of Changes Abbreviations Quick search: hover cursor over selection in Contents, and click the link to jump to correct page, this will facilitate your search. Any text in blue is also clickable.

Table of Contents

TABLE OF CONTENTS **2**

PTC TELEPHONE NUMBERS AND EMAIL ADRESSES **7**

GREAT ORMOND STREET CHILDREN'S HOSPITAL 7
THE ROYAL MARSDEN HOSPITAL 10
UCLH CHILDREN AND YOUNG PEOPLE'S CANCER SERVICES 12

ABBREVIATIONS **14**

CHAPTER LEADS, CO-LEADS AND CONTRIBUTORS **15**

1. FORWARD & SUMMARY OF SIGNIFICANT CHANGES **19**

1.1 FORWARD – 5TH EDITION V1.0 (MAR 2023) 19
1.2.1 SUMMARY OF CHANGES FOR SCP 5TH EDITION V1.1 (JULY 2023) [CHANGES HIGHLIGHTED IN YELLOW IN PROTOCOL] 22

2. USE OF BLOOD COMPONENTS AND HAEMATOPOIETIC CYTOKINES **32**

GENERAL INFORMATION 32
SPECIAL REQUIREMENTS 32
Irradiated blood components *33*
CMV negative components *34*
INDIVIDUAL BLOOD COMPONENTS 35
Red blood cells *35*
Platelets *36*
Platelet Transfusion Guidelines *38*
Fresh Frozen Plasma (FFP) *39*
Octaplas *39*
Cryoprecipitate *40*
Fibrinogen concentrate *40*
Major haemorrhage *41*
Granulocytes *41*
HAEMATOPOIETIC CYTOKINES 42
Granulocyte Colony Stimulating Factor (GCSF) *42*
Thrombopoietin Receptor Agonists (TPO-RA) *42*
Erythropoietin *42*

3. NEUTROPENIC SEPSIS / FEBRILE NEUTROPENIA **44**

3.1 INTRODUCTION 44
3.2 DEFINITION OF "NEUTROPENIC SEPSIS" 44
3.3 INPATIENT (IP) VERSUS OUTPATIENT (OP)/ HOMECARE CCLG FN MANAGEMENT PATHWAYS FOR PATIENTS WITH FEVERS OR SUSPECTED TO HAVE FEBRILE NEUTROPENIA 46
3.4 PATIENT ASSESSMENT 47
3.4.1 - Table 1: Assessment of patients with neutropenic sepsis *47*
3.5 FEBRILE NEUTROPENIA: OUTPATIENT (OP)/HOME CARE CCLG FN PATHWAY = CHILDREN'S CANCER AND LEUKAEMIA GROUP (CCLG) MANAGING FEBRILE NEUTROPENIA IN THE UK IN 2020 PROPOSED NEW MANAGEMENT PATHWAY V 1.01 APRIL 20 ... 48
3.6 FEBRILE NEUTROPENIA: INPATIENT (IP) PATHWAY 49
Flow diagram / Summary of the emergency management – Inpatient Pathway *49*
3.6.1. Empirical First-Line Antibiotics - to be administered within 1 hour *50*
3.6.1.1 GOSH microbiology data and resistance patterns. *51*
3.6.2. Special scenarios: *52*
i. 3.6.2.1 Clinically unstable and deteriorating patients ♦ (new presentation of sepsis) needing Intensive Care (Irrespective of renal function) *52*
ii. 3.6.2.2 Patients (clinically stable) with renal impairment or at risk of renal impairment *53*
iii. 3.6.2.3 Patients who are known to be colonised by resistant organisms *53*
iv. 3.6.2.4 Bone prosthesis *54*
v. 3.6.2.5 Meningitis *54*
vi. 3.6.2.6 VP (ventriculo-peritoneal) shunt *54*

vii. 3.6.2.7 Patient at risk of Gram-positive infection 54
viii. 3.6.2.8 Allergies 54
ix. 3.6.2.9 Pneumocystis jirovecii pneumonia (PJP) 54
x. 3.6.2.10 m.1555A>G (a.k.a. A1555G) 55
Drug doses and Therapeutic Drug Monitoring (TDM) 55
3.7 ONGOING MANAGEMENT - 48 HOURS ASSESSMENT - INPATIENT PATHWAY - NEUTROPENIC SEPSIS: 56
3.7.1. Microbiological documented infection 56
3.7.2. When to remove the Central Venous Catheters (CVC)? 57
3.7.3. When to change antibiotics? 57
3.7.4. When to stop iv antibiotics? 57
3.7.5. When to change to oral antibiotics? 58
3.8 DISCHARGE – INPATIENT PATHWAY 58
3.9 ONGOING MANAGEMENT (INPATIENT PATHWAY) - AFTER 96 HOURS INTRAVENOUS ANTIBIOTIC TREATMENT IF PERSISTENT FEVER 59
3.9.1 Invasive Fungal Diseases (IFD). 59
3.10 FEBRILE NON-NEUTROPENIA 61
3.11 REFERENCES 63

4. PREVENTION AND TREATMENT OF SPECIFIC INFECTIONS AND VACCINATIONS IN PATIENTS WHO HAVE RECEIVED CHEMOTHERAPY OR HAEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) 65

4.1 VARICELLA-ZOSTER 65
4.1.1 Vaccination of siblings/household contacts 65
4.1.2 VZV Post-exposure prophylaxis (PEP) 65
4.1.3 Definition of significant exposure to VZV 65
4.1.4 Special circumstances which may increase risk of VZV infection 66
4.1.5 Rationale for guideline 66
4.1.6 Figure 1: Management of patients with malignant disease until at least six months after completion of standard-dose chemotherapy or radiotherapy 67
4.1.7 Choice of VZV prophylaxis (Oral aciclovir or oral valaciclovir) 68
4.1.8 VZIG and contraindication to aciclovir/valaciclovir 69
4.1.9 Post autologous or allogenic HCST patients 69
4.1.11 Information to parents after aciclovir / valaciclovir prophylaxis or VZIG 70
4.1.12 Treatment of Clinical Varicella/ Herpes Zoster 70
4.1.13 Supportive care with intravenous (IV) aciclovir 70
4.2 HERPES SIMPLEX VIRUS 71
Management of patients with suspected oral herpes simplex 71
4.3 **MEASLES** 72
4.4 PJP - PNEUMOCYSTIS PNEUMONIA (FORMERLY KNOWN AS *PNEUMOCYSTIS CARINII PCP*) AND OTHER INTERSTITIAL PNEUMONIA ... 72
4.5 PREVENTION OF INFECTION AND VACCINATION POLICIES IN HAEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS 74
4.6 VACCINATIONS FOR PAEDIATRIC PATIENTS TREATED WITH STANDARD-DOSE CHEMOTHERAPY 74

5. DRUGS USED IN THE TREATMENT OF INFECTIONS (REMOVED) 75

6. ONCOLOGICAL EMERGENCIES 77

INTRODUCTION 77
ECTHYMA GANGRENOSUM/NECROTISING FASCIITIS 77
TUMOUR LYSIS SYNDROME 77
Figure 6.1 Tumour lysis syndrome flow chart 1: Prior to starting treatment/chemotherapy 78
Figure 6.2 Tumour lysis syndrome flow chart 2: After starting appropriate treatment/chemotherapy 79
Initial management = Prevention (..... 81
EMERGENCY MANAGEMENT OF HYPERKALAEMIA 82
LEUKOSTASIS AND HYPERLEUKOCYTOSIS 83
ANTERIOR MEDIASTINAL MASSES & SUPERIOR VENA CAVA (SVC) OBSTRUCTION 86
SPINAL CORD COMPRESSION (SCC) 88
- *Suggested dose of Dexamethasone intravenously or orally for raised ICP & spinal cord compression is 10mg/m2/day in divided doses.* 89

RAISED INTRACRANIAL PRESSURE 90
- *Suggested dose of Dexamethasone intravenously or orally for raised ICP & spinal cord compression is 10mg/m2/day in divided doses.* 90

SEIZURES AND STATUS EPILEPTICUS 91
ACUTE HYPERTENSION AND HYPERTENSIVE ENCEPHALOPATHY 91
INTESTINAL OBSTRUCTION AND TYPHLITIS 91
TYPHLITIS 92
PANCREATITIS 93
COAGULOPATHY/DIC 94
CARDIAC DYSFUNCTION & TAMPONADE 95
VENO-OCCLUSIVE DISEASE 97
EXTRAVASATION 97
POST-ASPARAGINASE OBSERVATIONS & MONITORING FOR ALLERGIC REACTIONS 98

7. CENTRAL VENOUS ACCESS DEVICES 102

TYPES OF CVADS 102
CARE OF THE TUNNELLED AND NON-TUNNELLED CVADS 104
Aseptic Non-Touch Technique (ANTT) 104
Assessing and maintaining patency 105
EXIT SITE CARE 106
BATHING, SHOWERING AND SWIMMING 107
TROUBLESHOOTING 107
Occlusions 107
Withdrawal occlusion 108
Total occlusion 108
Catheter damage 108
Protocol / Standard Operating Procedure (SOP) for Urokinase administration (if appropriate, use alteplase or alternatives as per local policies & protocols) 108
References 111

8. EXTRAVASATION 113

WHAT IS EXTRAVASATION? 113
Infiltration 113
Flare 114
VESICANT DRUGS AND SOLUTIONS REPORTED TO CAUSE EXTRAVASATION INJURY: 115
RISK FACTORS FOR INFILTRATION AND EXTRAVASATION 116
RECOGNITION OF INFILTRATION / EXTRAVASATION 117
PREVENTION OF INFILTRATION/EXTRAVASATION 118
NURSING RESPONSIBILITIES WHEN ADMINISTERING INTRAVENOUS MEDICINES 118
Monitoring of the infusion 119
MANAGEMENT OF INFILTRATION AND EXTRAVASATION 119
THIS IS A MEDICAL EMERGENCY ANYTIME OF THE DAY OR NIGHT 119
Extravasation Kit 121
Saline washouts (Flush out Technique) 121
REFERENCES/BIBLIOGRAPHY 122

9. NUTRITION INTERVENTION IN PAEDIATRIC ONCOLOGY & HAEMATOLOGY PATIENTS 125

THE AIMS OF NUTRITIONAL SUPPORT IN PAEDIATRIC ONCOLOGY PATIENTS ARE 125
CAUSES OF NUTRITIONAL PROBLEMS IN ONCOLOGY PATIENTS 125
Nutritional screening and referral 125
Children identified as being "at risk" of malnutrition or malnourished 125
NUTRITIONAL STRATEGIES 126
Oral Intake 126
*Table 9.1 Examples of nutritional supplements (prescription only) * 127*
ENTERAL FEEDING 128
Table 9.2 Types of Enteral Feeds 129*
Table 9.3 Semi elemental/ elemental/peptide-based feeds 130*
Parenteral Nutrition (PN) 130
Alternative /Complimentary diets and Supplements 131
HEALTHY, BALANCED EATING 131
EXCESSIVE WEIGHT GAIN AND POOR EATING HABITS 132

REFERENCES 132

10. MOUTH CARE PROTOCOL AND ORAL MUCOSITIS 134

ORAL AND DENTAL ASSESSMENT 135
WHO analgesic ladder (1986) 138
OTHER SUPPORTIVE THERAPIES 138
REFERENCES: 139

11. HYPERTENSION 143

MEASUREMENT OF BLOOD PRESSURE IN CHILDREN: 143
CURRENT DEFINITION OF HYPERTENSION: 143
MANAGEMENT OF HYPERTENSION: 144
HYPERTENSIVE CRISIS / ACUTE HYPERTENSIVE ENCEPHALOPATHY: 145
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES): 146
DRUGS USED IN THE TREATMENT OF HYPERTENSION (REFER TO BNFC FOR DOSES) 146
REFERENCE: 148
NEONATES: ESTIMATED BP, AFTER 2 WEEKS OF AGE, IN INFANTS FROM 26-44 WEEKS POST-CONCEPTUAL AGE 149
BOYS: BLOOD PRESSURE TABLE (FLYNN JT, KAELBER DC, BAKER-SMITH CM, ET AL. *PEDIATRICS.* 2017) 150
GIRLS: BLOOD PRESSURE TABLE (FLYNN JT, KAELBER DC, BAKER-SMITH CM, ET AL. *PEDIATRICS.* 2017) 153

12. BASIC PRINCIPLES OF SYMPTOM MANAGEMENT 157

12.1 INTRODUCTION 157
12.2 DRUG DOSES USED FOR SYMPTOM / PALLIATIVE CARE MANAGEMENT 158
The Association of Paediatric Palliative Medicine Master Formulary (APPM Formulary) 158
12.3 NAUSEA AND VOMITING 159
Antiemetics and sites of action 160
Nausea and vomiting during therapy 160
Nausea and vomiting in palliative care 160
Table 12.1 Cytotoxic agents and emetic risk 161
12.4 CONSTIPATION 163
Pathway for treatment of constipation 164
12.5 PAIN 165
Causes of pain during the disease process 165
12.5.1 Assessment of Pain 165
12.5.2 Definitions of pain 166
12.5.3 Management of pain 167
12.5.3.1 Approaches to Pain Management 167
12.5.3.2 WHO approaches to paediatric analgesia 168
12.5.3.3 Analgesics 168
12.5.3.4 Opioids 169
12.5.3.5 Management of acute (procedure-related) and persisting pain ON Systemic Anti-Cancer Therapy (SACT), targeted therapy or radiotherapy treatment 171
12.5.3.6 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): 172
12.5.3.7 Pain Management OFF Treatment (ie with sustained count recovery): 172
12.5.3.8 Management of neuropathic pain 172
12.5.3.9 Bone pain 172
12.5.3.10 Headaches 173
12.5.3.11 Pain due to raised intracranial pressure 173
12.6 DYSPNOEA 173
12.7 SWEATING 173
12.8 SEIZURES 173
12.9 ANXIETY AND AGITATION 174
12.9 TERMINAL RESTLESSNESS 174
12.10 RETAINED RESPIRATORY TRACT SECRETIONS 174
12.11 BLEEDING 174
12.12 SYRINGE DRIVERS 175

Jump to Contents Summary of Changes Abbreviations Quick search: hover cursor over selection in Contents, and click the link to jump to correct page, this will facilitate your search. Any text in blue is also clickable.

13. MANAGEMENT OF FLUIDS AND ELECTROLYTES 177

CAUSES OF FLUID AND ELECTROLYTE IMBALANCE IN PAEDIATRIC ONCOLOGY 177
ELECTROLYTE DISTURBANCES 178
Sodium 178
Potassium 183
Calcium 187
Magnesium 190
Phosphate 191
SPECIFIC FLUID BALANCE PROBLEMS IN ONCOLOGY PATIENTS 193
Diabetes Insipidus 193
CHAPTER 13 - APPENDIX A 194
Normal Daily Electrolyte Requirements 194
Calculation of Electrolyte Deficit 194
General Rules for Intravenous Electrolyte Administration 194
CHAPTER 13 - APPENDIX B 195
Fluid Balance 195
Calculation of Fluid Requirements 195
Resuscitation fluids 197
Electrolyte concentrations - intravenous fluids[5] 200
Electrolyte content - gastro-intestinal secretions[5] 200
REFERENCES 201

14. MANAGEMENT OF LATE EFFECTS IN SURVIVORS OF CHILDHOOD CANCER 203

GONADOTOXICITY, FERTILITY IMPAIRMENT AND FERTILITY PRESERVATION 203
Males 203
Females 203
Fertility preservation options: 204
LATE EFFECTS IN SURVIVORS OF CHILDHOOD CANCER 205
Patient Pathway 207
Aims of long-term follow-up 207
Survivors of childhood cancer at follow-up should have an opportunity to discuss the following 208
Table 14.1 Summary of clinical history, examination and surveillance investigations 209
CHAPTER 14 - APPENDIX A 211
Treatment Summary and Long Term Follow Up Plan 211
Systems at Risk and Care Plan 213
Surveillance Required 215
REFERENCES 216

15. SOCIAL AND FINANCIAL SUPPORT AVAILABLE TO FAMILIES 219

SUPPORTING PATIENTS AND FAMILIES 219
ACCESSING HELP 219
FINANCIAL ASSISTANCE 220
Welfare reform 220
Disability Living Allowance (DLA) for Children 221
Personal independence Payment 221
Special rules for Disability Living Allowance/PIP 221
Carers Allowance (CA) 222
Debt management 222
OTHER ORGANISATIONS OFFERING SUPPORT: 223
USEFUL PUBLICATIONS 227

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Abbreviations

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ANTT	Aseptic Non-Touch Technique
ATG	anti-thymocyte globulin
BAL	Bronchioalveolar lavage
BC	Blood cultures
BM	bone marrow
BMT	Bone Marrow Transplant
BNF	British National Formulary (adult version)
BNFc	Children's British National Formulary
CATS	Children's Acute Transport Service
CCLG	Children's Cancer and Leukaemia Group
CMV	Cytomegalovirus
CNS	Clinical nurse specialist
CNS	Central nervous system
CVAD	Central Venous Access Devices
CVC	Central venous catheter
DIC	disseminated intravascular coagulation
ESBL	Extended-spectrum beta-lactamases
ext	extension
FFP	Fresh Frozen Plasma
FN	Febrile neutropenia (Neutropenic sepsis)
G6PD	glucose-6-phosphate dehydrogenase
GCS	Glasgow Coma Scale
GCSF	Granulocyte Colony Stimulating Factor
GOSH	Great Ormond Street Hospital
GvHD	graft versus host disease
Hb	haemoglobin
HLA	Human Leucocyte Antigen
HNIG	Human Normal Immune globulin
HSCT	Hematopoietic stem cell transplant
ICP	Intracranial pressure
IV	intravenous
IVIG	intravenous immune globulin
LCH	Langerhans cell histiocytosis
LFT	Liver Function Tests
LP	Lumbar Puncture
MCT	medium chain triglycerides
MHRA	Medicines and Healthcare products Regulatory Agency
MRCP	Magnetic resonance cholangiopancreatography
MRSA	methicillin-resistant Staphylococcus aureus
NGT	nasogastric tube
NHL	Non-Hodgkin's Lymphoma
NHSBT	National Health Service Blood and Transplant
NICE	national institute for health and care excellence
NJT	nasojejunal tube
PBSC	peripheral blood stem cells
PBSCT	peripheral blood stem cell transplant
PEP	Post exposure prophylaxis
PHE	Public Health England
PICU	Paediatric Intensive Care Unit
PN	Parenteral nutrition
POSCU	Paediatric Oncology Shared Care Units
PTC	Primary Treatment Centre or Principal Treatment Centre
RMH	Royal Marsden Hospital
TA-GvHD	transfusion-associated graft versus host disease
SaBTO	Safety of Blood, Tissues and Organs
SCC	Spinal cord compression
SCP	Supportive care protocols
SHOT	Serious Hazards of Transfusion
STRS	South Thames Retrieval Service
SVC	Superior Vena Cava
TBI	total body irradiation
TLS	Tumour lysis syndrome
TPO-RA	Thrombopoietin Receptor Agonists
UCLH	University College London Hospital
vCJD	variant Creutzfeldt-Jakob Disease
VOD	Veno-occlusive disease
VP	ventriculoperitoneal
VZIG	Varicella zoster immune globulin

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And thank you to all other contributors who assisted the Chapter leads and co-leads.

1.

Forward and Summary of Significant Changes

1. Forward & Summary of Significant Changes

Quick Search Function
Similar to last edition, the electronic version of this document has a built-in quick search function.

For your assistance, in order to find your page or section, go to Contents (pages 2 to 6), and click the link to jump to correct page, this will facilitate your search.

At the top of every page, there is a "Jump to Contents". Clicking on this will take you back to the Contents pages. "Summary of Changes" will take you to section 1.2.

All "Text in Blue" can also be clicked to jump/hyperlink to the referred section or external reference.

1.1 Forward – 5th Edition v1.0 (Mar 2023)

5th edition v1.0 (Mar 2023) was a planned update of these Supportive Care Protocols.

As always, updating this collection of protocols was a massive task; it was only possible through the effort and dedication from all the Chapter Leads, Co-Leads and Contributors. I'd like to this opportunity to thank everyone involved.

Yours gratefully.

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13th March 2023

Forward - 4th Edition v3.1 amendment (Dec 2020)

Version 3.1 is intended to be a short amendment. The full protocol update is scheduled for 2022.

April 2020, CCLG published Children's Cancer and Leukaemia Group (CCLG) Managing Febrile Neutropenia in the UK in 2020 Proposed New Management Pathway v 1.01 April 2020. [CCLG FN pathway] (Last read 16/12/2020). At the time, this pathway was widely distributed to all PTCs & POSCUs, it was stated that all PTCs & POSCUs were to follow the CCLG pathway. After weeks of discussion, we've finally completed the amendment of Chapter 3. The CCLG FN pathway is now incorporated in this chapter, which all PTCs & POSCUs should follow. This CCLG FN pathway replaced the Low-Risk Febrile Neutropenia and Febrile Non-Neutropenia sections of Chapter 3.

Due to recent updates in transfusion practices, Chapter 2 has also been updated to reflect this.

I am grateful for the advice from the Drs Sujith Samarasinghe, James Soothill, Alasdair Bamford, Keith Sibson and Orlagh McGarrity at GOSH, and input from RMH and UCLH teams for this amendment.

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16th December 2020

Forward - 4th Edition v3.0 (2020)

A recent case highlighted several gaps in Chapter 3 Neutropenic Sepsis protocol, such as septic patients may present with unexplained abdominal or generalised pain without fever. Clinical teams need to be aware to look for other signs of sepsis.

Secondly, due to high incidence of Gram-negative bacteria resistant to Piperacillin/tazobactam and Ciprofloxacin at GOSH (by inference antibiotic resistance may also be an issue for other PTCs and POSCUs), then acutely deteriorating patients, especially needing PICU, the combination of Piperacillin/tazobactam and Ciprofloxacin is not adequate for such septic patients.

This chapter has been updated to clarify recommendations in such patients, even in presence of renal impairment.

I am grateful for the advice from the microbiologists, ID and nephrology at GOSH and input from RMH and UCLH for this update.

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12th February 2020

Forward - 4th Edition v2.0 (2018)

I am extremely grateful to all the lead authors, editors and contributors for their time and effort. Updating these guidelines is definitely not something that can be done by one person.

We started the process of discussing this update since December 2017. Unfortunately the update of some of the sections, in particular chapters 3 and 4, has been incredibly complex. For those who attended the POSCU Educational Study Day on 22/5/2018, I presented the major changes agreed for v2.0. Unfortunately, subsequently there had been further spanners thrown in the works, therefore we had to re-discuss and make more changes.

One of the major changes in this update is removing majority of drug doses and other national guidelines from this version. There are dissent in some quarters, however BNFc/BNF can change at a rapid rate; moreover in the past 24 months, there are 2 separate national guidelines which have made 2 updates each already. As mentioned above, much effort is needed every time this SCP is updated, thus it is not realistic to keep up with the updates of the BNFc and various national guidelines.

Lastly, I'd like to express again my sincere appreciation to all contributed.

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10th October 2018

Forward - 4th Edition v1.0 (2014)

Within the London area the three principal treatment centres (PTCs), the paediatric shared care centres (POSCUs) and community nursing teams, provide a high quality, comprehensive treatment for children with cancer. While the PTCs are responsible for the cancer treatment, the POSCUs and community teams deliver much of the supportive care that many children receive. The supportive care guidelines were written to ensure the POSCUs and community teams follow the same (as far as possible) practice to facilitate consistent, optimal treatment of children with cancer and blood diseases.

These supportive care guidelines have been produced collaboratively between the three London PTCs (Royal Marsden, GOSH, UCLH) and representatives from POSCUs. This is the fourth edition of the protocol (previous editions were produced in 2003, 2007 and 2011).

The current supportive care protocol 4th edition v1.0 (2014) was produced following extensive revision incorporating up to date evidence, national and/or local guidelines for management. No new chapters have been added. However, the chapters have been reshuffled with the "Oncological Emergencies" chapter being moved to a more prominent position (Chapter 6 instead of Chapter 12 previously). All the guidelines have been revised, sometimes after a lot of debate.

Wherever possible the PTCs have agreed uniform guidelines, although some differences remain between centres. These differences have been clearly highlighted in the document. For some issues where there are both lack of concrete evidence and strong bias in different doctor's personal practice, it was just not possible to come to a complete consensus between the 3 PTCs. For POSCUs and community teams who share care with more than one PTC, these differences may cause confusion, I can only apologise on behalf of all 3 PTCs.

Please see below for significant changes that have been made in the new edition.

I hope that everyone involved in the shared management of children will find the protocol useful. We will continue to produce regular updates and any suggestions or comments will be very welcome. Please email: danny.cheng@gosh.nhs.uk.

Lastly, I want to thank all the lead authors and contributors who have put in a huge amount of effort to make this revision possible. A special thanks to Sonja Tattermusch who edited and formatted the protocol.

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27th May 2014 (Date of final approval)

1.2.1 Summary of changes for SCP 5th edition v1.1 (Jul 2023) [Changes highlighted in yellow in protocol]

5thed v1.1 Jul 2023	Very brief update on prolonged/continuous household exposure to VZV. **Chapter 4 – Prevention & treatment of infections / vaccinations** (Chapter lead: Dr Richa Ajitsaria, consultant paediatrics, Hillingdon) **4.1.4 Special circumstances which may increase risk of VZV infection:** expanded & clarified prolonged continuous household exposure/contact. Consider separating patient from index case and/or identify other non-VZV immune household members. **4.1.7 Choice of VZV prophylaxis:** clarified PEP for prolonged household exposure.

1.2.2 Summary of changes for SCP 5th edition v1.0 (March 2023) [Changes highlighted in yellow in protocol]

5thed v1.0 Mar 2023	All of following changes were agreed by all 3 PTCs. **Chapter 2 - Use of blood components** (Chapter lead: Dr Keith Sibson, consultant, GOSH) **Page 33 Irradiated blood components:** reorganised list, hopefully clearer patient groups. **Page 34 CMV negative blood components:** UCLH patients still follows SaBTO, but added note: "Any potential alloHSCT patients should have CMV serological status checked at referral to the haematology service, but this is for future reference only" **Page 38 Platelet transfusion thresholds:** 1) RMH standard LP threshold 40x10^9/L; 2) ♦Note A2G re: 1st diagnostic LP: as per A2G/ALLTogether trial for ALL patients (Procedural Guideline for CSF sampling and processing section), "platelet count should be >50 x10^9/L for the first (subsequent LPs can use a lower threshold according to local practice)" **Chapter 3 – Neutropenic sepsis / Febrile neutropenia** (Chapter leads: Dr P Angelini, consultant, RMH; Dr L Ferreras-Antolin, consultant, St George's U.H.) • General reorganisation of chapter, together with new flow diagrams, hopefully this chapter is now easier to read and follow. **Suggest read this entire chapter very carefully.** Highlights of changes are: **Page 50 empirical 1st line IVAB:** UCLH (non-sarcoma, non-bone tumour) now changed to piperacillin/tazobactam and amikacin **Page 55 m.1555A>G (aka A1555G):** Untested or patients with pending result for m.1555A>G: Use standard first line empirical antibiotics (ie piperacillin / tazobactam with aminoglycosides) whilst result is pending. (ie this includes newly diagnosed cancer patients at POSCU or GOSH; as well as patients whose test had been sent, but results are pending). Refer to Section 3.6.2.10 for rationale and details. **Page 61 febrile non-neutropenia:** this section was removed from last version. It is recognised that this section is still needed. **Chapter 4 – Prevention & treatment of infections / vaccinations** (Chapter lead: Dr Richa Ajitsaria, consultant paediatrics, Hillingdon) **4.1 Varicella-Zoster:** this section was updated. Please read carefully.

4.1.13 Supportive care with intravenous (IV) aciclovir: relatively common for patients on IV aciclovir to develop renal impairment. Recommend IV maintenance fluids when IV aciclovir.
4.2 Herpes Simplex Virus: new section on HSV and management of oral HSV infection.
4.4 Pneumocystis Pneumonia (PJP): updated

Chapter 6 – Oncological emergencies

(Chapter lead: Dr Danny Cheng, locum consultant/associate specialist, GOSH)

Page 81 TLS: added paragraph re: some subtypes of M4/M5 AML may develop low K with TLS

Page 98 Post-Asparaginase observations & monitoring for allergic reactions: recent data reported relatively high incidence of post asparaginase reactions, especially within 1st 2 hours, and subsequent 2-6 hour and 6-24 hour periods. Hence, SOP to guide PTC, POSCU and parental monitoring.

Chapter 7 – Central Venous Access Devices

(Chapter leads Johanna Lee & Jessica Price, practice educators, GOSH)

- Entire chapter significantly updated. Please read carefully.

Page 108 SOP for Urokinase administration: updated. Please read carefully.

Chapter 9 – Nutrition

(Chapter lead: Louise Henry, advanced dietetic practitioner, RMH)

- Entire chapter significantly updated. Please read carefully.

Chapter 10 – Mouthcare

(Chapter lead: Charlotte Humphrey, practice educator, GOSH)

- Please read carefully.

Chapter 12 – Symptom management

(Chapter lead: Bhumik Patel, senior specialist pharmacist in paediatric palliative care, GOSH)

Page 171 Management of acute (procedural-related) and persisting pain ON SACT, targeted therapy or radiotherapy treatment: paracetamol may be used as analgesia to outpatients / daycases / patient at home. This is irrespective of neutrophil count. Although, there is strict guidance for usage, refer to this section for details.

Chapter 14 – Management of Late Effects

(Chapter lead: Dr Vesna Pavasovic, consultant, GOSH)

Page 203 Gonadotoxicity, fertility impairment and fertility preservation: new section. Please read.

1.3 Summary of changes for SCP 4th edition v3.1 (December 2020)

4th edition v3.1 Dec 2020	All of following changes were agreed by all 3 PTCs. **Chapter 2 amended by Dr Keith Sibson (GOSH Haematology consultant)** **Page 31 CMV negative blood components:** UCLH now follows SaBTO (as agreed by Dr Vicky Grandage, UCLH Consultant Haematologist) **Pages 35 – 36 FFP, Octaplas and Cryoprecipitate** **Source, shelf-life and storage:** updated with national transfusion practice. **Chapter 3 amended by:** Dr Danny Cheng (GOSH Associate Specialist) Dr Alasdair Bamford (GOSH Infectious Diseases consultant) Dr James Soothill (GOSH Microbiology consultant) Orlagh McGarrity (GOSH Antimicrobial Pharmacist) **CCLG FN pathway replaced the Low-Risk Febrile Neutropenia and Febrile Non-Neutropenia sections of Chapter 3.** **3.2 (p 40) Definition of "Neutropenic Sepsis"** wording clarified and changed to: "Any patient with or WITHOUT fever who has features suggestive of systemic infection should be treated with intravenous antibiotics, i.e. even if numerical definition of 1) and 2) above has not been met." **3.3 (p 41) CCLG FN pathway** - Children's Cancer and Leukaemia Group (CCLG) Managing FN in the UK in 2020 Proposed New Management Pathway v 1.01 April 2020 **3.4 (p 42) New flowchart** for: Inpatient (IP) versus Outpatient (OP) Management Pathways for patients with Fevers or suspected to have Febrile Neutropenia **3.4 (p 43) Table 1: "Assessment of patients with neutropenic sepsis":** added reference to Sepsis 6 and CCLG FN pathway **3.6.1 (p 46) GOSH patients only: new cancer diagnosis with unknown A1555G:** clarified that if piperacillin/tazobactam and ciprofloxacin were used, then if blood cultures are negative at 24 hours and the patient has no clinical evidence of infection other than fever, then ciprofloxacin should be stopped. (Consistent with aminoglycoside stopping recommendation as per section 3.6.2) **3.6.1 (p 46) First line empirical treatment differs from standard empirical treatment:** clarified recommendation that patients' medical records should be clearly documented with personalised "first line intravenous antibiotics" plan; this plan need to be easily accessible to all staff in case of emergency presentation. **3.6.2 (p 47)** Recommendation to stop aminoglycoside or ciprofloxacin (if used as dual antibiotic therapy) treatment early, ie at 24 or 48 hours from initiation of therapy, provided blood cultures are negative and if clinically appropriate.

1.4 Summary of changes for SCP 4th edition v3.0 (2020)

4th edition v3.0 (2020)	**4th edition v3.0 (2020) Chapter 3 amended by:** Dr Danny Cheng (GOSH Associate Specialist) Drs John Hartley, Garth Dixon & James Hatcher (GOSH Microbiology consultants) Dr Alasdair Bamford (GOSH Infectious Diseases consultant) and Dr Steve Marks (GOSH Nephrology consultant) And subsequently agreed by Royal Marsden and University College Hospital PTCs **3.2 (p40)** added septic patients may present with abdo pain, hypothermia or without fever **3.5 (p44)** added to flow chart "afebrile, hypothermia or abdo pain" presentation and acute deteriorating and/or needing PICU irrespective of renal function refer to Section 3.6.3 **3.6.1 (p45)** added avoid aminoglycosides except deteriorating patients needing PICU **3.6.1 (p46)** added GOSH antibiotic resistance data. If allergy to beta-lactams, then suggest cipro & amik (instead of Cipro & gent in v2.0). If no alternative and must use Cipro & gent, then POSCU to be vigilant and be aware of antibiotic resistant sepsis if clinical deterioration **3.6.3 (p48) *Clinically deteriorating patients, needing intensive care (Irrespective of renal function or A1555G result).*** Piptazobactam & ciprofloxacin is NOT adequate for deteriorating patient needing PICU 1) First choice: **Piperacillin/tazobactam** with ***aminoglycosides (*see renal note)** 2) Second choice: **Carbapenem** with ***aminoglycosides (*see renal note)** 3) or if necessary, discuss with PTC consultant, microbiology and/or renal team **3.6.4 (p49)** Patients with renal impairment, only if they are clinically stable and NOT acutely septic, then Piperacillin/tazobactam and ciprofloxacin may be appropriate. Regular reviews and if patient deteriorate, then use recommendations as per 3.6.3. **Chapter 4 (p66)** Note that CCLG published Dec 2019 update of "Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy and HSCT Recipients"

1.5 Summary of Significant change between SCP 4th edition v2.0 and v1.0

4th edition v2.0 (2018)	**General – Removal of majority of drug doses and other guidelines** - SCP is not a formulary - electronic BNFc & BNF are updated regularly (could be as frequent as monthly) - often confusion when there is a discrepancy between BNFc and SCP - for convenience, the only drug doses retained in v2.0 are some of the emergency drugs (eg neutropenic sepsis antibiotics) or doses not found or differs from BNFc (eg TLS drugs, dexamethasone for spinal cord compression etc) - However even for the drugs doses remaining in these SCP guidelines, if BNFc decides to update and change, we recommend to follow BNFc - There are also growing number of other national guidelines (such as PHE for VZV and Measles, CCLG vaccination guidelines) and BMT guidelines specific to each PTCs. The groups that write these guidelines update regularly and the authors of these SCP are not informed of these updates. - Where our recommendation differs from these guidelines, then we have included in these SCP. Otherwise refer to the external guidelines.

4th edition v2.0 (2018)	**Chapter 2: Use of Blood Components and haemopoietic cytokines** Lead: Dr Keith Sibson, consultant haematology, GOSH (Keith.Sibson@gosh.nhs.uk) - Blood products order by volume, ie in ml's and not in "unit(s)" based on British Society of Haematology guidelines - Retinoblastoma added to keep platelets >30x10^9/L - GOSH patients only: platelet threshold for lumber puncture & trephine >20x10^9/L - UCLH and RMH patients: platelet threshold remains the same for lumber puncture and trephine
4th edition v2.0 (2018)	**Chapter 3: Treatment of Infections in the neutropenic or immunosuppressed patient** Lead: Dr Paola Angelini, consultant oncology, RMH (paola.angelini@nhs.net) - BMT patients: irrespective of neutrophil counts, all post BMT patients should be treated using the neutropenic sepsis guidelines when it is **less than 12 months** post BMT (previously 6 months) - LFTs, lactate and blood gases only when indicated (no longer compulsory) - Added Echinocandins (micafungin or caspofungin) as alternative to iv antifungals - Combined standard risk NS & low risk NS flow charts: 3.4 Flow diagram / Summary of the emergency management of neutropenic sepsis - Appendix : Summary for Empirical antimicrobial choices - Section 3.8.1 and Section 3.8.2 (prev protocol conflicting & discrepancy with 37.5C and 38.0C used in different parts of protocol). **Now unified - stop IV antibiotics if** : ➢ Patient afebrile (<38.0°C) for 48hrs ➢ All blood cultures are negative **AND** no clinical focus of infection ➢ Patient is clinically well **AND** patient was not clinical septic/compromised at presentation ➢ Clinical judgement that patient is safe to stop antibiotics - Expanded on section 3.6.3 regarding "Patients at risk of renal impairment", this group now includes, hepatoblastoma, osteosarcoma, medulloblastoma, renal tumours, high risk neuroblastoma during COJEC induction, infant ependymoma. For this group of patients: - Patients with established renal impairment, recommend follow 3.6.3.2 (Piperacillin / tazobactam +/- ciprofloxacin or discuss with microbiology) - Bone tumour patients, follow 3.6.1 (Piperacillin / tazobactam with ciprofloxacin, if endoprosthesis in situ, add teicoplanin. No change from previous guideline) - **Oncology patients with normal renal function but at risk of renal impairment.** Unless individual patient's discharge or clinic letters specifically state alternative regimen in correspondence to POSCUs, then standard first line neutropenic sepsis antibiotics remain the same as per 3.6.1 (ie Piperacillin / tazobactam and aminoglycoside) for all patients with normal renal function but under group of "at risk of renal impairment" section 3.6.3.1 (hepatoblastoma, medulloblastoma, renal tumours, Wilms tumour, high risk neuroblastoma during COJEC induction, infant ependymoma). This is same policy as patients with carriage of multi-drug resistant organisms. - GOSH oncology team will audit this practice and outcome (when using aminoglycoside sparing regimens irrespective of renal function)

	- General reformatting, including flowcharts for standard risk and low risk FN etc.
4th edition v2.0 (2018)	**Chapter 4: *Prevention and Treatment of Specific Infections*** Lead: Dr Richa Ajitsaria, consultant paediatrics, Hillingdon (richa.ajitsaria@nhs.net) - Post VZV PEP (post exposure prophylaxis), major changes to recommendation. Authors had already made decision to change first line VZV PEP from VZIG to aciclovir. Subsequent PHE Aug 2018 publication stated that VZIG was no longer available for PEP unless aciclovir/valaciclovir contraindicated. This confirmed the authors' decisions. Thus this chapter has been significantly amended. - Added supportive care (hydration and monitor renal function) when using oral/iv aciclovir, or valaciclovir. (orals sections 4.7.4 and iv aciclovir 4.12) - **Measles IVIG PEP** refer to Public Health England: Guidelines on Post-Exposure Prophylaxis for measles (August 2017) Gateway number: 2017250 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/637003/Guidance_for_measles_post-exposure_prophylaxsis.pdf [last read 9/10/18] or refer to subsequent and more up to date versions. - Removed: **Prevention of Infection and vaccination policies in Haematopoietic Stem Cell Transplant Recipients**. To avoid duplication of policies, please refer to individual PTC BMT unit's policy. - Removed: **Vaccinations for Paediatric Patients treated with Standard-Dose Chemotherapy.** To avoid duplication of policies, please refer to the most up to date version of Children's Cancer and Leukaemia Group: Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy And Haemopoietic Stem Cell Transplantation (HSCT) Recipients (Authors: Dr Soonie R.Patel, Professor Rod Skinner and Professor Paul T.Heath) https://www.cclg.org.uk/member-area/treatment-guidelines/supportive-care
4th edition v2.0 (2018)	**Chapter 5: Drugs used in the treatment of infections** Removed
4th edition v2.0 (2018)	**Chapter 6: Oncological Emergencies** Lead: Dr Danny Cheng, Associate Specialist, GOSH (danny.cheng@gosh.nhs.uk) - .Dexamethasone for **spinal cord compression & raised ICP** (no doses in BNFc) Suggested dose of **Dexamethasone** intravenously or orally for raised ICP & spinal cord compression is **10mg/m2/day in divided doses.** This can be divided into 2 to 3 doses, up to maximum capped dose of 4mg per dose 4 times daily (ie 16mg in 24 hours) o Note: there is no publish data on recommended doses of dexamethasone for raised ICP or spinal cord compression. This dose is based on discussions with and recommendations from neuro-oncologists and neurosurgeon at GOSH*. This dose

	can be adjusted according to response in liaison with PTC and neurosurgeons. - Useful reference for subsequent management of spinal cord injury: **National Spinal Injuries Centre - Stoke Mandeville Hospital: Bowel management following spinal cord injury. May 2007** (last read 10/10/18)
4th edition v2.0 (2018)	**Chapter 7: Care of Central Venous Access Devices** Lead: Jo Davison, Oncology Nurse Specialist, Hillingdon (jodavison@nhs.net) - simplified and clarified - If access of Implantable Port is unsuccessful, then discard needle and use new needle for subsequent attempt. (Previous version stated port needle could be reuse for second attempt)
4th edition v2.0 (2018)	**Chapter 9: Nutrition intervention in Paediatric Oncology & Haematology Patients** Lead: Louise Henry, Senior Dietitian, RMH (Louise.Henry@rmh.nhs.uk) - Simplified and clarified
4th edition v2.0 (2018)	**Chapter 10: Mouth Care Protocol and Mucositis** Lead: Kristy McKeon, Specialist Nurse, Whipps Cross (Kristy.mckeon@bartshealth.nhs.uk) - simplified and clarified - Based on evidence from this published literature, GelclairTM is recommended if patients develop significant oral mucositis
4th edition v2.0 (2018)	**Chapter 11: Hypertension** 4th edition v1.0 original author: Dr Mary Taj, Consultant Oncologist, RMH (Mary.Taj@icr.ac.uk) - Removed drug doses. Otherwise no change.
4th edition v2.0 (2018)	**Chapter 12: Basic principles of symptom management** Lead: Bhumik Patel, Senior Specialist Pharmacist in Paediatric Palliative Care, GOSH (Bhumik.Patel@gosh.nhs.uk) - Removed drug doses. Refer to BNFc or **APPM** Formulary http://www.appm.org.uk/resources/APPM+Master+Formulary+2017+-+4th+edition.pdf - Updated chemo emetogenic risk table 11 as per CCLG anti-emetics guidelines v1.0 (March 2018) - Oral morphine dose when used for Management of acute (procedure-related) and persisting pain: Removed "starting at 50% of lowest BNFc starting dose". It is felt that this is subtherapeutic and replaced with For prescribing Morphine, follow the lowest standard starting dose in the BNFc. Some clinicians may want to prescribe 'low dose' morphine which is considered lowest starting dose as recommend by BNF for children and then titrate accordingly. - **Constipation:** *Recommendation based on NICE guidelines with modification for haem/onc patients*
4th edition v2.0 (2018)	**Chapter 13: Management of fluids and electrolytes** 4th Edition v1.0 original author: Dr Lynley Marshall, Consultant Oncologist, RMH (Lynley.Marshall@rmh.nhs.uk) v2.0 edited by: Dr Danny Cheng,

	- Removed drug doses. - Some drugs do not have doses in BNFc, thus the doses from previous 4th edition v1.0 has been retained, but added note "to be used under guidance and direction of experts and specialists" - Added section in Appendix on Electrolyte contents of gastrointestinal secretions - Otherwise unchanged
4th edition v2.0 (2018)	**Chapter 14: Management of late effects in survivors of childhood cancer** Lead: Dr Paola Angelini, consultant oncology, RMH (paola.angelini@nhs.net) - Simplified and clarified

1.6 Summary of Significant change between SCP 4th edition v1.0 and previous 3rd edition (Supportive Care Protocol version 5.0 August 2011)

<table>
<tr><td>4th edition v1.0 (2014)</td><td>Chapter 2: Use of Blood Components and haemopoietic cytokines

CMV negative components
Regrettably, the 3 PTC's have different approaches in adopting the guidelines from Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). Refer to this section for details.</td></tr>
<tr><td>4th edition v1.0 (2014)</td><td>Chapter 3: Treatment of Infections in the neutropenic or immunosuppressed patient

Neutropenic sepsis/Febrile neutropenia protocol
Please read this chapter carefully. Extensive changes have been made based on evidence reported in "Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients" National Institute for Health and Clinical Excellence Clinical Guideline (NICE clinical guideline 151 - published in Sept 2012. http://guidance.nice.org.uk/cg151 - last read on 14/4/14)

<table>
<tr><th>Description of change</th><th>Previous guidance (SCP 5.0 Aug 2011)</th><th>New guidance SCP 4th edition v1.0</th></tr>
<tr><td>Definition of neutropenia</td><td>< 0.75 x 10^9/l</td><td>0.5×10^9/l or lower</td></tr>
<tr><td>Definition of fever</td><td>Fever > 38° C:
• for > 4 hours or
• twice at least 4 hours apart
Fever > 38.5°C once</td><td>38° C or higher</td></tr>
</table>

Initial monotherapy is not recommended for any patients even for those with neutrophils above 0.5 x 10^9/l in view of the frequency of piptazobactam resistant organisms among PTC patients in London.

Febrile non-neutropenia Protocol
Treatment of fever in immunosuppressed patients without neutropenia
Expanded with new guidance.</td></tr>
</table>

	In response to comments from POSCUs after the publication of Supportive Care Protocol Version 5.1 (updated 9th May 2014 Protocol Amendment Replacing pages 16 to 29 of Supportive Care Protocol v5.0 August 2011) – some minor changes have been made to the neutropenic sepsis section. (Comparing with v5.1)
4th edition v1.0 (2014)	**Chapter 6: Oncological emergencies** **Tumour lysis syndrome** In patients at low risk of TLS, avoid hyperhydration till 12 to 24 hours prior to start of treatment. Risk of iatrogenic problems outweighs the small risk of TLS in low-risk category. **Leukostasis and Hyperleukocytosis** For patients with high count leukaemia and at high risk of leukostasis (determined by PTC consultant), then the POSCU consultant will need to arrange immediate intensive care (CATS/STRS) transfer. The patient should arrive at PICU within **2 hours** of referral to PTC. Refer to this section for details of other changes.
4th edition v1.0 (2014)	**Chapter 11: Drug treatment of hypertension** The chapter has been reviewed and edited. The main changes are that the table of drug doses is now in keeping with BNF-C
4th edition v1.0 (2014)	**Chapter 12: Basic Principles of symptom management** **Pain and codeine** **Management of acute (procedure-related) and persisting pain** **ON chemotherapy, targeted therapy or radiotherapy treatment** **Off treatment (ie with sustained count recovery)** Significant change in practice is introduced in the usage of paracetamol and second line analgesia for the management of pain in neutropenic patients. Please read this section carefully. The rationales for change are: In July 2013, the MHRA published a Drug Safety Update restricting the use of codeine in children under 12years because of concerns over morphine toxicity. It also restricted the use of codeine in patients aged 12-18 years with obstructive sleep apnoea. The WHO guidelines (2012) no longer recommend the use of codeine as a weak opioid for the management of persisting pain in children due to similar concerns over its metabolism. Subsequently a joint statement relating to the use of codeine issued by RCPCH and other associated professional bodies were published in Nov 2013.
4th edition v1.0 (2014)	**Chapter 15: Social and financial support available to families** There are major changes between the versions. Please treat as a completely new document

2.

USE OF BLOOD COMPONENTS AND HAEMATOPOIETIC CYTOKINES

Chapter leads: Dr Keith Sibson, consultant haematology, GOSH (Keith.Sibson@gosh.nhs.uk)
Rachel Moss, transfusion practitioner, GOSH (Rachel.Moss@gosh.nhs.uk)

Contributor: Dr Danny Cheng, associate specialist/locum consultant, GOSH (danny.cheng@gosh.nhs.uk)

2. Use of blood components and haematopoietic cytokines

Introduction

Transfusion practice has advanced over the last 2 decades, particularly with respect to improved safety measures introduced to reduce the risk of transfusion transmitted infections. Additional safety enhancements have been put in place specifically for neonatal & paediatric blood components. Nevertheless, care should always be taken to ensure that blood components are only transfused when necessary and that the most appropriate component is used for each individual patient in any given situation.

The following guideline deals with common scenarios in paediatric haematology/oncology when blood components (red cells, platelets, granulocytes and plasma) need to be administered. The detailed use of manufactured blood products (such as immunoglobulin, albumin and specific clotting factor concentrates) will not be discussed.

General Information

Medical and nursing staff become very familiar with administering blood components to children with malignant diseases. However, it should always be remembered that families with no previous experience of blood transfusion can be very concerned about its safety and may require much explanation and reassurance. Information leaflets should be offered to the family and informed consent should be obtained before a child receives their first transfusion, just as would be done prior to administration of chemotherapy. NHS Blood & Transplant (NHSBT) leaflets are available via the Transfusion Practitioner or to download from the website:
NHSBT Hospitals and Science > Patient Services > Patient Blood Management > Patient Information Leaflets

- **Receiving a blood transfusion**

  The leaflet encompasses red cells, platelets and plasma components and is suitable for adult patients, carers, and the parents of babies and children

- **Amazing You**

  Explains to young children about blood, red cells, white cells and platelets.

- **Voyages on the microsub discovery**

  This is aimed at older children and explains why a blood transfusion may be needed.

- **Information for patients needing irradiated blood**

  This leaflet contains a sticker for the front of the child's notes and a card that should be completed and handed to the parents

Special Requirements

Patients with certain conditions will require special components. Each PTC and POSCU should have robust systems in place to ensure that their blood transfusion laboratory and all staff treating these patients are aware of their special requirements prior to the first transfusion being administered and at the point in treatment where the requirements may change. The London Regional Transfusion Committee has produced

shared care documents which may be used to facilitate communication of these requirements (click to follow link): London RTC Working Groups (transfusionguidelines.org)

Irradiated blood components

All cellular blood components have been leucocyte depleted in the UK since 1999. However, residual lymphocytes can cause fatal transfusion-associated graft versus host disease (TA-GvHD) in patients who are severely immunocompromised. Irradiation of blood components at 25Gy effectively inactivates these lymphocytes, thus preventing this complication from occurring.

1. **Non-irradiated red cells or platelets:**
   - if **NOT** listed in box 2. below, then there is **NO** need to give irradiated red cells or platelets.

2. **The following groups of patients must always receive irradiated red cells and platelets:**
   - All patients with Hodgkin lymphoma
     - continue indefinitely
   - All patients treated with regimens containing purine analogue drugs
     - fludarabine, cladribine (2-cda), deoxycoformycin, clofarabine, nelarabine & bendamustine
     - continue indefinitely
   - All patients treated with anti-thymocyte globulin (ATG)
     - continue indefinitely
   - All patients treated with alemtuzumab (Campath)
     - continue indefinitely
   - All recipients of allogeneic bone marrow (BMT) or peripheral blood stem cell transplant (PBSCT)
     - start from the initiation of conditioning chemo/radiotherapy
     - continue for the duration of GvHD prophylaxis or until lymphocytes >1x10^9/l
     - continue indefinitely if chronic GvHD present or on-going immunosuppression is required
   - All donors of bone marrow (BM) or peripheral blood stem cells (PBSC)
     - from 7 days prior to / during the harvest
   - All patients undergoing BM or PBSC harvesting for future autologous re-infusion
     - from 7 days prior to / during the harvest
   - All patients undergoing autologous BMT or PBSCT
     - start from the initiation of conditioning chemo/radiotherapy
     - continue until 3 months post-transplant
     - or 6 months post-transplant if total body irradiation (TBI) was used in conditioning
   - All cases where there may be a shared haplotype between the donor and the recipient
     - donations from first or second-degree relatives
     - HLA-matched platelets
   - Neonates who have previously received blood components in utero (IUT)
     - Continue until 6 months after the expected date of delivery
   - Children with severe T lymphocyte immunodeficiency syndromes, such as
     - Combined Immunodeficiency (CID)
     - Severe Combined Immunodeficiency (SCID)
     - 22q11 Deletion Syndrome (DiGeorge Syndrome / Velo-Cardio-Facial Syndrome)
     - Wiskott-Aldrich Syndrome

Following is standard blood bank practice (clinicians are not required to give extra instructions)

3. **Granulocyte transfusions should always be irradiated.**
4. It is **not** necessary to irradiate fresh frozen plasma or cryoprecipitate.

CMV negative components

In March 2012, the Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) released a new position statement on Cytomegalovirus (CMV) testing of blood components. This concluded that leucodepletion of blood components (routine since 1999) offers sufficient protection against the risk of CMV transmission in most patient groups and that CMV negative components should no longer be considered necessary for CMV negative patients undergoing chemo/radiotherapy or requiring allogeneic haematopoietic stem cell transplant (alloHSCT). (www.dh.gov.uk/health/2012/03/sabto/)

Some BMT teams do not fully agree with this statement and feel that there is still a significant risk of CMV transmission when transfusing blood components from CMV positive donors to CMV negative alloHSCT recipients.

Regrettably, therefore, there are currently different guidelines for patients being managed by each of the PTCs, as follows:

Royal Marsden patients	**UCLH patients**	**GOSH patients**
No need to give CMV negative components at any stage	**No** need to give CMV negative components.	*Patients **NOT** planned to have alloHSCT:* **No** need to give CMV negative components.
Follow the SaBTO recommendations from diagnosis throughout therapy	Follow the SaBTO recommendations from diagnosis throughout therapy	Follow the SaBTO recommendations from diagnosis throughout therapy
Give standard leucodepleted components regardless of CMV status	(Any potential alloHSCT patients should have CMV serological status checked at referral to the haematology service, but this is for future reference only)	*Patients **confirmed** that they **will undergo** alloHSCT:* Require CMV negative components IF patient's CMV IgG status is negative*

***Further details for GOSH patients only:**

- **For GOSH patients who are confirmed that they will undergo alloHSCT:**
  - Review pre-transfusion CMV status
  - If CMV IgG negative, then give CMV negative components
  - Otherwise, no need for CMV negative components
- **For GOSH patients who are undergoing/have undergone alloHSCT and have a protocol stating that they require CMV negative blood components during and post-transplant:**
  - adhere to this protocol
- **For all other GOSH haematology / oncology patients:**
  - give standard leucodepleted components regardless of CMV status. ***ie majority of haem/onc (non-BMT) patients DO NOT require CMV negative blood components.***

Importantly, even if CMV negative components are said to be required, do not delay emergency platelet / blood transfusion for clinically significant bleeding if CMV negative components are not immediately available.

For completeness, it should be noted that SaBTO also concluded that CMV negative blood components **should** continue to be provided for the following:

- Pregnant women (planned transfusions), intra-uterine transfusions, neonates
- Granulocyte transfusions (as these can obviously never be leucodepleted) to patients who are CMV IgG negative and are receiving, or may in the future receive an allogeneic transplant from a CMV IgG negative donor, unless the risks of delay / unavailability outweigh the benefits

Individual Blood Components

Red blood cells

Indications:

- Top up transfusions due to disease / treatment
  - usual threshold is 70 g/l
  - always check patient protocol, as some will have a higher threshold (e.g. children with thalassemia major) whilst some may have a lower threshold
  - in children undergoing radical radiotherapy, aim for haemoglobin around 120 g/l
  - if symptomatic from anaemia at a level above their usual threshold, usually appropriate to transfuse on clinical grounds
  - **beware newly presenting patients with high count leukaemia (see below)**

- Anaemia due to bleeding
  - if significant on-going bleeding, transfuse on clinical grounds
  - refer to local major haemorrhage protocol

Dose:

- Calculate the desired rise in haemoglobin (Hb):
  - Desired rise = target Hb (g/l) – actual Hb (g/l)

- Then calculate the dose of red cells:
  - Dose in millilitres = desired rise (g/l) x 0.4 x weight (kg)

- Request this volume from the transfusion laboratory
  - If this volume slightly exceeds that of an appropriate unit of red cells by a clinically insignificant amount, the dose should be rounded down to the volume of this unit (so as not to waste the majority of a second unit)
  - Paedipacks (6 packs divided from one adult unit) are available for small volume transfusions; these reduce wastage and limit donor exposure

- Prescribe the red cells in millilitres at a maximum rate of 5 ml/kg/hr

Precautions:

- **Newly presenting patients with high count leukaemia (>50 x10^9/l)**
  - discuss urgently with PTC consultant
  - risk of worsening leukostasis with red cell transfusion
  - if required, do not give more than 5 ml/kg over 4 hours
  - rarely need to raise Hb to >60 g/l
  - for more details, see chapter 6 on emergencies

- Transfusion reactions
  - see local guidelines for management (NB: may require reporting to SHOT and MHRA)

Shelf-life and storage:

- 35 days (or 14 days post-irradiation)
- Stored at 4°C (+/- 2°C), transfusion must be started within 30 minutes of removal from fridge

Platelets

Indications:

- Top up transfusions
  - see flow diagram on next page

- Prior to surgical procedures
  - see flow diagram on next page

- Active bleeding
  - aim to keep platelet count >50 x10^9/l
  - or >100 x10^9/l if bleeding at critical site (e.g. lungs / CNS)

Dose:

- 10 ml/kg, up to a maximum of 1 standard unit

- Administer over 30-60 minutes (i.e. 10-20 ml/kg/hr)

- Double doses may rarely be required in the following circumstances:
  - Active bleeding
  - Sepsis / DIC
  - Splenomegaly

- In these patients, platelet counts may need to be checked every few hours to identify when to administer the next transfusion and to decide if a double dose is required

Precautions:

- **It is extremely rare for platelet transfusions to be contraindicated and they should never be withheld if a patient has life-threatening bleeding with a low platelet count**

- They may, however, become relatively ineffective due to poor increments:
  - in practice, defined as:
  - failure to rise >20-30 x10^9/l at 1 hour or 10-20 x10^9/l at 24 hours post-transfusion

- If clinical / numerical concern about poor response to platelet transfusions:
  - document 1 hour / 24-hour increments
  - check for potential non-immune causes (see above) and treat appropriately
  - if no cause identified, send samples to NHSBT to test for HLA antibodies
  - if HLA antibodies identified, request HLA matched platelets (this requires the NHSBT to call up specific donors, so needs forward planning and regular communication)
  - monitor increments as before and inform NHSBT of results
  - if good response, continue with effective donors
  - if poor response, take advice from Consultant in NHSBT

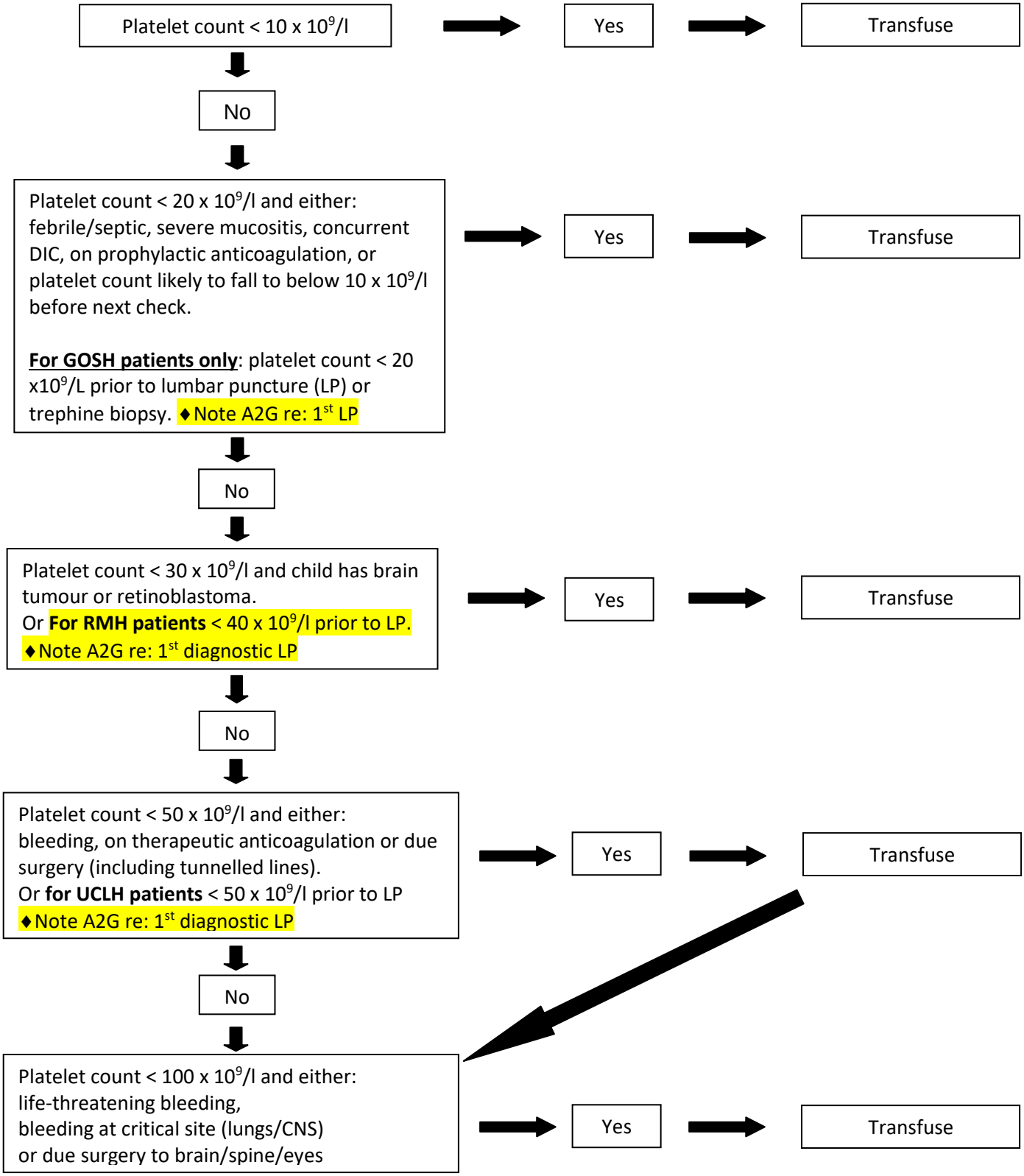
Shelf-life and storage:

- 7 days at 22°C (+/- 2°C) with continuous gentle agitation

Platelet Transfusion Guidelines

Haematology/Oncology patients at presentation / on treatment

(Children with non-malignant causes of thrombocytopenia excluded)



♦Note A2G re: 1st diagnostic LP: as per A2G/ALLTogether trial for ALL patients (Procedural Guideline for CSF sampling and processing section), "platelet count should be >50 x10^9/L for the first lumbar puncture (subsequent LPs can use a lower threshold according to local practice)"

Fresh Frozen Plasma (FFP)

Indications:

- Correction of coagulopathy due to:
  - DIC / severe sepsis
  - severe liver disease
  - major haemorrhage
  - severe vitamin K deficiency (give vitamin K as well)
  - reversal of warfarin (if prothrombin complex concentrate not available / not advised)
  - clotting factor deficiencies if specific concentrate not available (e.g. Factor V deficiency)

- Usually FFP is given to correct a coagulopathy if a child is bleeding or requires a surgical procedure

- Occasionally warranted to correct a very severe (or rapidly worsening) coagulopathy in the absence of bleeding/surgery, e.g. new presentation of leukaemia (especially AML)

- Correction of coagulopathy with FFP in other situations is rarely needed

- FFP should **not** be given as a volume expander

- **Discussion with a consultant haematologist is advised in the following situations:**
  - Rapidly worsening coagulopathy
  - Major haemorrhage
  - Reversal of warfarin
  - Specific clotting factor deficiencies

Dose:

- 10-15ml/kg over 30-60 minutes

- If this volume slightly exceeds that of an appropriate unit (or units) of FFP by a clinically insignificant amount, the dose should be rounded down to the volume of this unit / these units

Source, shelf-life and storage:

- Sourced from untransfused, male, UK donors
- Can be stored for 3 years at -25°C or below
- Once thawed, can be stored in the fridge (4°C) for up to 5 days before transfusion

Octaplas

- Alternative source of plasma
  - pharmaceutically produced pooled human plasma
  - sourced from countries with low vCJD risk, solvent detergent treated (viral inactivation)
- Each unit is exactly 200ml
- Can be stored for 4 years at -18°C or below
- Once thawed, can be stored in the fridge for up to 5 days
- But once removed from the fridge, must be transfused within 8 hours

Cryoprecipitate

Indications:

- Correction of a low fibrinogen level due to:
  - DIC / severe sepsis
  - severe liver disease
  - major haemorrhage
  - congenital hypofibrinogenaemia / afibrinogenaemia (if fibrinogen concentrate unavailable)

- Usually given to correct a low fibrinogen if a child is bleeding or requires a surgical procedure

- Occasionally warranted to correct a very low (or rapidly falling) fibrinogen in the absence of bleeding/surgery, e.g. new presentation of leukaemia (especially AML)

- Correction of fibrinogen with cryoprecipitate in other situations is rarely needed

- Occasionally used as a rich source of factor VIII and von Willebrand factor (if specific factor concentrates not available)

Dose:

- Initially 5ml/kg over 30 minutes

- Young children may require 10ml/kg

Source, shelf-life and storage:

- Sourced from UK donors
  - each individual unit is approx. 50ml in volume
  - pooled units (from 5 UK donors) are available for larger children
- Can be stored for 3 years at -25°C or below
- Once thawed, must be kept at room temperature and used within 4 hours

Fibrinogen concentrate

- A blood product, pharmaceutically manufactured from human plasma
- Can be used to correct low fibrinogen levels in the same situations as cryoprecipitate
- Requires discussion with consultant haematologist
- NB: Does not contain other clotting factors!

Major haemorrhage

- As well as requiring large volumes of red cells, patients will become severely thrombocytopenic and coagulopathic

- Patients need monitoring of blood counts and clotting screens aiming for:

  - platelet count > 75 x10^9/l
  - APTT ratio <1.5
  - INR <1.5
  - Fibrinogen >1.5 g/l

- Some patients benefit from having a much higher fibrinogen level (e.g. >2-3 g/dl)

- Recombinant factor VIIa (NovoSeven) is **no longer considered safe or effective** in this situation and **should not be used**

- Please consult your local major haemorrhage protocol for more details specific to your hospital and always involve your consultant haematologist in any major haemorrhage

Granulocytes

- Clear evidence for their benefit is lacking, but they are sometimes used for patients with severe neutropenic sepsis, unresponsive to antibiotics / GCSF

- Will always be administered at the PTC (following decision made by the patient's PTC Consultant)

- To request pooled granulocytes from the NHSBT:
  - Discuss case with NHSBT Consultant
  - If agreed, requests must be made by 3pm for granulocytes to be delivered the following day (usually will arrive by 4pm)
  - PTC transfusion laboratory can liaise directly with NHSBT laboratory for subsequent requests on the same patient
  - They will **not** be available on Sundays, Mondays or the day following a Bank Holiday

- **Administration of granulocytes:**
  - Plan to transfuse as soon as possible after collection
  - If there is an unavoidable delay, granulocytes can be stored at room temperature (must **not** be agitated or refrigerated) until midnight on the day of collection
  - Granulocytes must be irradiated
  - Pre-medicate the patient with paracetamol and chlorphenamine
  - If previous reactions, also use hydrocortisone
  - Dose is max 10-20 ml/kg
  - Infuse over 1-2 hours through a standard red cell giving set

Haematopoietic Cytokines

Granulocyte Colony Stimulating Factor (GCSF)

GCSF is commonly used following allogeneic bone marrow transplant and high dose therapy with autologous stem cell rescue, as well as prior to stem cell harvest. It is also used routinely in some protocols to support dose intensive therapy. In addition, its use should be considered in the following situations and every case should be discussed with the responsible consultant:

- Febrile neutropenic episodes not responding to antibiotics and antifungals within an expected timeframe
- Neutropenic patients with extensive cellulitis, necrotising fasciitis, peri-anal infections or severe fungal infections
- Clinically deteriorating patients with neutropenic sepsis
- Patients who have had severe delays in previous chemotherapy courses due to neutropenia

GCSF may be administered intravenously over 30 minutes, or by subcutaneous injection.

Thrombopoietin Receptor Agonists (TPO-RA)

Two TPO-RA (romiplostim and eltrombopag) are licensed for use in adults and children (over the age of 1 year) with chronic refractory immune thrombocytopenia (ITP). There is emerging evidence for the use of these agents to support the platelet count in selected patients with chemotherapy-induced bone marrow suppression. However, they are not licensed for this purpose and their use cannot currently be recommended in this scenario.

Erythropoietin

Erythropoietin is used particularly for patients with anaemia due to chronic renal failure. However, there is insufficient evidence to support its use in children with anaemia due to malignant disease or its treatment.

3.

TREATMENT OF INFECTIONS IN THE NEUTROPENIC OR IMMUNOSUPPRESSED PATIENT

Including Neutropenic sepsis/febrile neutropenia

and

Treatment of fever in immunosuppressed patients without neutropenia

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3. Neutropenic Sepsis / Febrile Neutropenia

Throughout this chapter, the terms "neutropenic sepsis" & "febrile neutropenia" are used synonymously.

3.1 Introduction

Children with cancer are at increased risk of infection as a result of their disease and/or its treatment. Fever with neutropenia is the commonest manifestation of infection in children with cancer; such infection is potentially fatal. Febrile neutropenia is a medical emergency requiring urgent investigation and the administration of intravenous empirical antibiotic therapy within 1 hour. Aggressive use of inpatient intravenous antibiotic therapy has reduced morbidity and mortality rates and reduced the need for intensive care management.

This chapter is written taking into account of local microbiological sensitivities/resistance and incorporating recommendations based on "Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients" (NICE clinical guideline 151 - published in Sept 2012. http://guidance.nice.org.uk/cg151 - last read 20/1/2023.) April 2020, CCLG published Children's Cancer and Leukaemia Group (CCLG) Managing Febrile Neutropenia in the UK in 2020 Proposed New Management Pathway v 1.01 April 2020. [CCLG FN pathway] (Last read 20/1/2023). For the Supportive Care Protocols 4th Ed v3.1 (Dec 2020) update, this chapter was updated to include reference of this CCLG FN pathway, Aus Score, Home care Eligibility Assessment and Home Care Pathway, which all PTCs & POSCUs should follow. This replaced the Low-Risk Febrile Neutropenia section of this chapter. This CCLG FN pathway remains the same for Supportive Care Protocols 5th Ed v1.0 (Mar 2023) update

3.2 Definition of "Neutropenic Sepsis"

Diagnose neutropenic sepsis in patients having anticancer treatments whose:

1) Neutrophil count is 0.5 x 10^9 per litre or lower and who have either:
2) A temperature higher or equal to 38°C (by any measurement) **or**
3) Other signs or symptoms consistent with clinically significant sepsis

Any patient with or WITHOUT fever who has features suggestive of systemic infection should be treated with intravenous antibiotics, i.e. even if numerical definition of 1) and 2) above has not been met.

- **Unexplained generalised or abdominal pain, unexplained vomiting, hypothermia etc, may be signs of sepsis**
- **Look for other signs of sepsis (abnormal vitals, lactate, gas or end organ compromise etc)**

Neutropenia in children and young people with cancer

- A fever documented at home by parents requires the same urgent treatment as a fever recorded in hospital.
- Any patient who is febrile and could be neutropenic should be seen and assessed immediately by a doctor, nurse practitioner or nurse consultant trained in the management of children and young people with cancer.
- If a child is febrile and the neutrophil count is not known at presentation, the patient must be assessed immediately while awaiting the results of the urgent full blood count and other investigations initiated as indicated in Section 3.4.1 Table 1 Assessment of patients with neutropenic sepsis.
- If a child is febrile and the neutrophil count is higher than 0.5 x 10^9/L and there are other concerning clinical risk factors such as significant mucositis, patients with Down syndrome or an HSCT patient, consider starting empirical antibiotics.
- Classic signs of sepsis may be masked by steroids, e.g. during ALL induction and delayed intensification. If in doubt for an unwell child on steroids, start empirical antibiotics.
- Afebrile patients may still have sepsis. Hypothermia, unexplained abdominal or general pain could also be presentation of sepsis. Look for other signs of sepsis (eg other abnormal vital signs/observations, prolonged capillary refill time, raised lactate, abnormal blood gases, respiratory, cardiovascular, renal or liver compromise)
- Fever may sometimes develop during transfusion of blood products. Patients should be carefully assessed to decide whether such fevers are due to Transfusion Reaction or sepsis. If patient clinically appears septic, then manage as per Neutropenic Sepsis.

3.3 Inpatient (IP) versus Outpatient (OP)/ Homecare CCLG FN Management Pathways for patients with Fevers or suspected to have Febrile Neutropenia

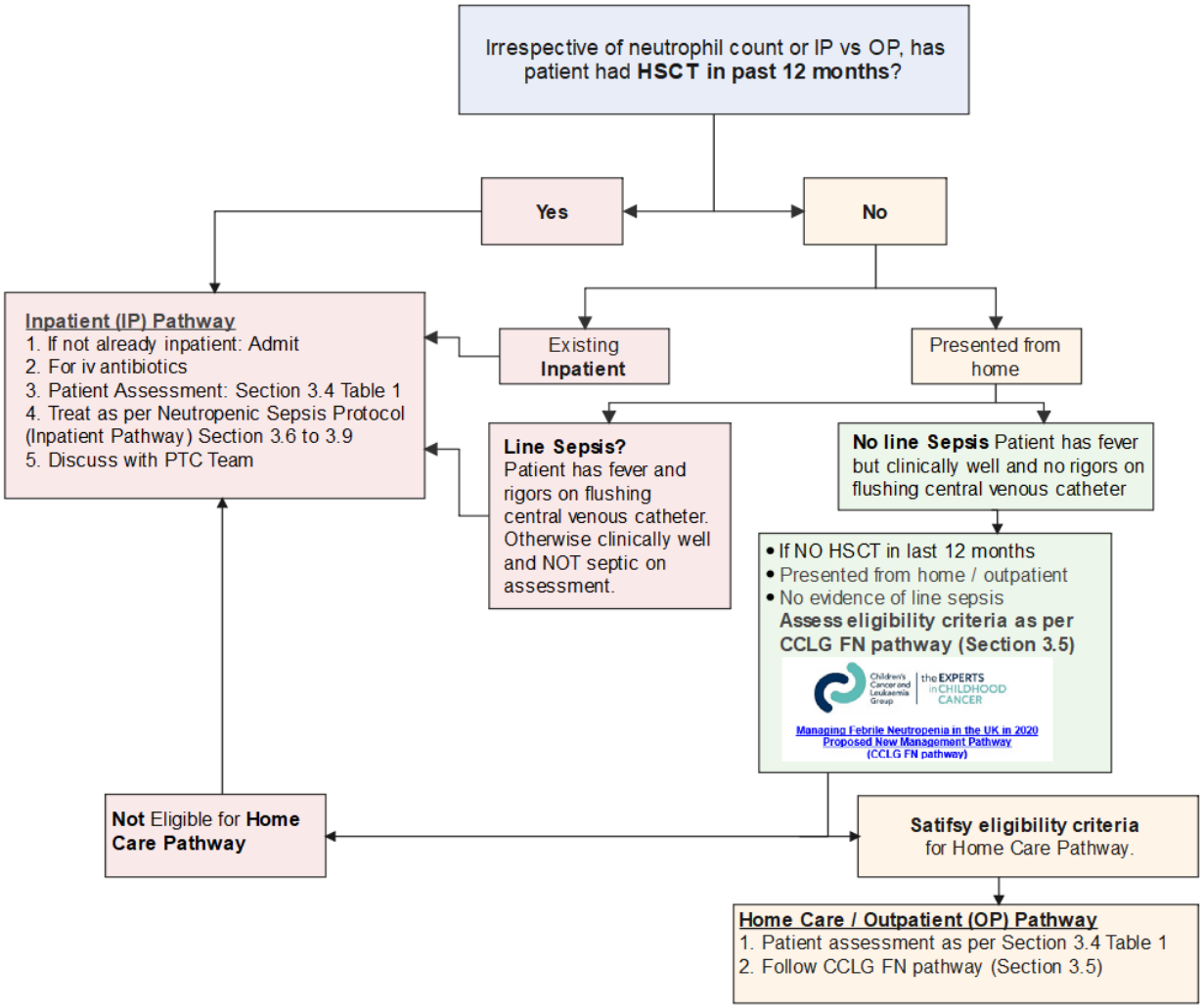
1. **Fever without neutropenia: refer to Section 3.10 Febrile Non-Neutropenia**

2. **Patients with neutropenia, follow flow diagram below for**

Section 3.5: Febrile Neutropenia: Outpatient (OP)/ Homecare CCLG FN pathway

Vs

Section 3.6 to 3.9: Febrile Neutropenia: Inpatient (IP) Pathway



3.4 Patient Assessment

3.4.1 - Table 1: Assessment of patients with neutropenic sepsis

- **Afebrile patients may still have sepsis**
- **Unexplained generalised or abdominal pain, unexplained vomiting, hypothermia etc, may be signs of sepsis**
- **Look for other signs of sepsis (abnormal vitals, lactate, gas or end organ compromise etc)**

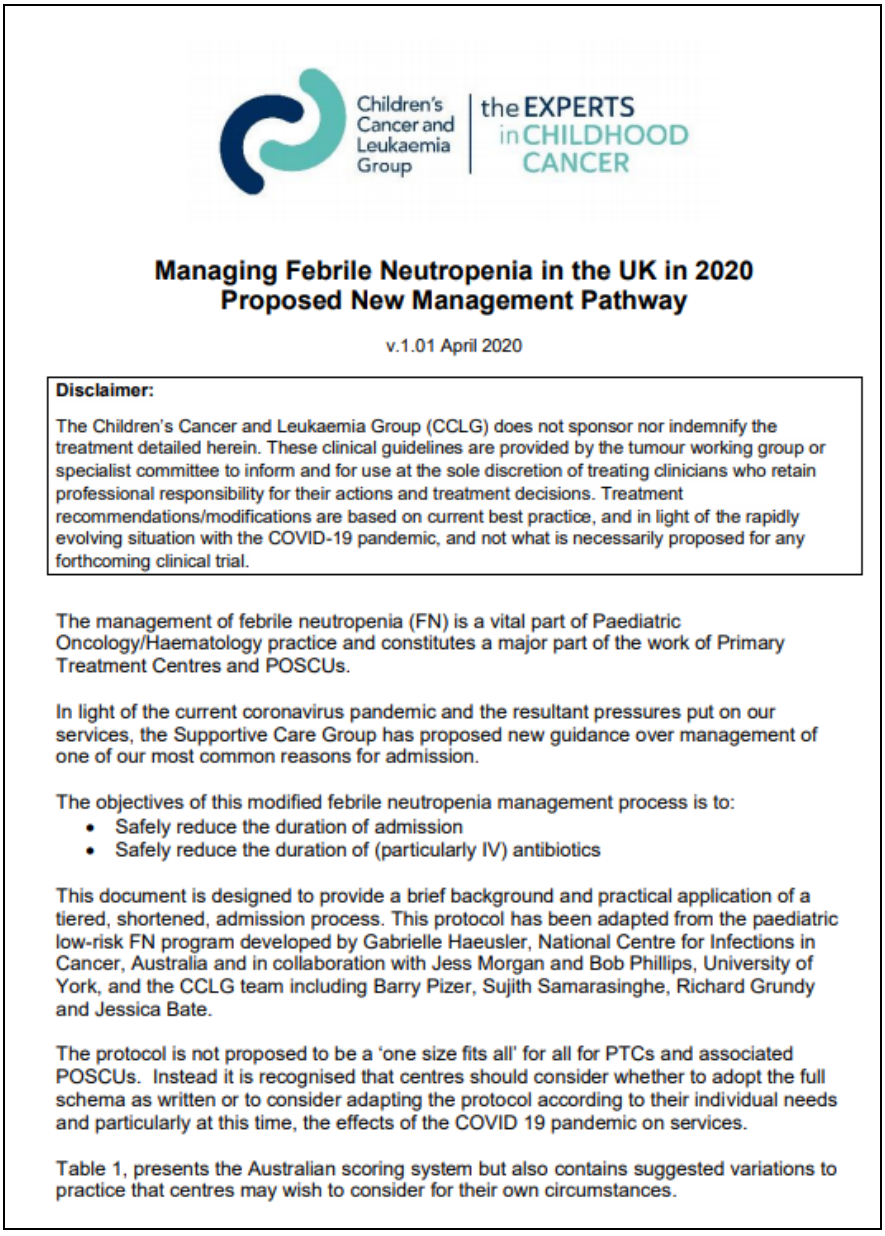
The initial clinical assessment of all patients with febrile neutropenia should include the following:

Assessments for all patients	
Detailed history and examination	To include ears, throat (looking for signs of mucositis) and examination of central venous access device for exit-site or tunnel infection, endoprostheses for signs of local infection. Ask about / examine perianal area.
Sepsis 6	As part of neutropenic sepsis assessment, please follow your local sepsis-6 policy, or if there is no local sepsis-6 policy, then refer to the tools and guidelines from The UK Sepsis Trust https://sepsistrust.org/professional-resources/clinical-tools/
Scoring system to assess patient's risk of septic complications	If appropriate as per Section 3.3, assess AUS Score and Eligibility for home care using **CCLG FN pathway**
Blood cultures	From each lumen of central venous access device Peripheral blood culture if no central venous access device. Blood volume: **according to local guidelines on minimal blood volumes.** **If no local policy, use :** Volume: 1ml (<19 kg), 3-4 ml (up to 30 kg), 5-6 ml (up to 50 kg), 5-10ml (>50kg)
Full blood count & differential	To be sent urgently
Other blood tests	Kidney function tests, C-reactive protein
Urinalysis and urine culture	For patients < 5 years or patients with urinary symptoms
Peri-anal swap/stool culture	As per local policy. **Looking for colonization by resistant MRSA or Gram-negative bacteria***
Assessments to consider	
Other blood tests	If indicated, liver function test and albumin (LFT's). If no clinical concerns, Do NOT send LFT's as part of routine neutropenic sepsis work up. Lactate if patient significantly unwell
Chest x-ray	Only in presence of respiratory symptoms or signs
Stool	For culture and virology if acute diarrhoea Consider *Clostridium difficile* screening (Follow local policy for admission stool screening)
Sputum/nasopharyngeal aspirate	If signs/symptoms of respiratory tract infection, send respiratory panel PCR.
Swabs for culture	From sites of clinical infection only

3.5 Febrile Neutropenia: Outpatient (OP)/Home care CCLG FN pathway = Children's Cancer and Leukaemia Group (CCLG) Managing Febrile Neutropenia in the UK in 2020 Proposed New Management Pathway v 1.01 April 2020 (last read 23/1/2023).

- All users must read the **CCLG FN pathway**, and refer to Section 3.4 below to understand how this pathway is incorporated into this Supportive Care Protocols document.

- To avoid this chapter becoming out of date when CCLG publishes updates and revisions, the CCLG FN pathway has not been pasted into this document. Refer to www.cclg.org.uk website for most up to date version.



Children's Cancer and Leukaemia Group | the EXPERTS in CHILDHOOD CANCER

Managing Febrile Neutropenia in the UK in 2020
Proposed New Management Pathway

v.1.01 April 2020

Disclaimer:

The Children's Cancer and Leukaemia Group (CCLG) does not sponsor nor indemnify the treatment detailed herein. These clinical guidelines are provided by the tumour working group or specialist committee to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations/modifications are based on current best practice, and in light of the rapidly evolving situation with the COVID-19 pandemic, and not what is necessarily proposed for any forthcoming clinical trial.

The management of febrile neutropenia (FN) is a vital part of Paediatric Oncology/Haematology practice and constitutes a major part of the work of Primary Treatment Centres and POSCUs.

In light of the current coronavirus pandemic and the resultant pressures put on our services, the Supportive Care Group has proposed new guidance over management of one of our most common reasons for admission.

The objectives of this modified febrile neutropenia management process is to:

- Safely reduce the duration of admission
- Safely reduce the duration of (particularly IV) antibiotics

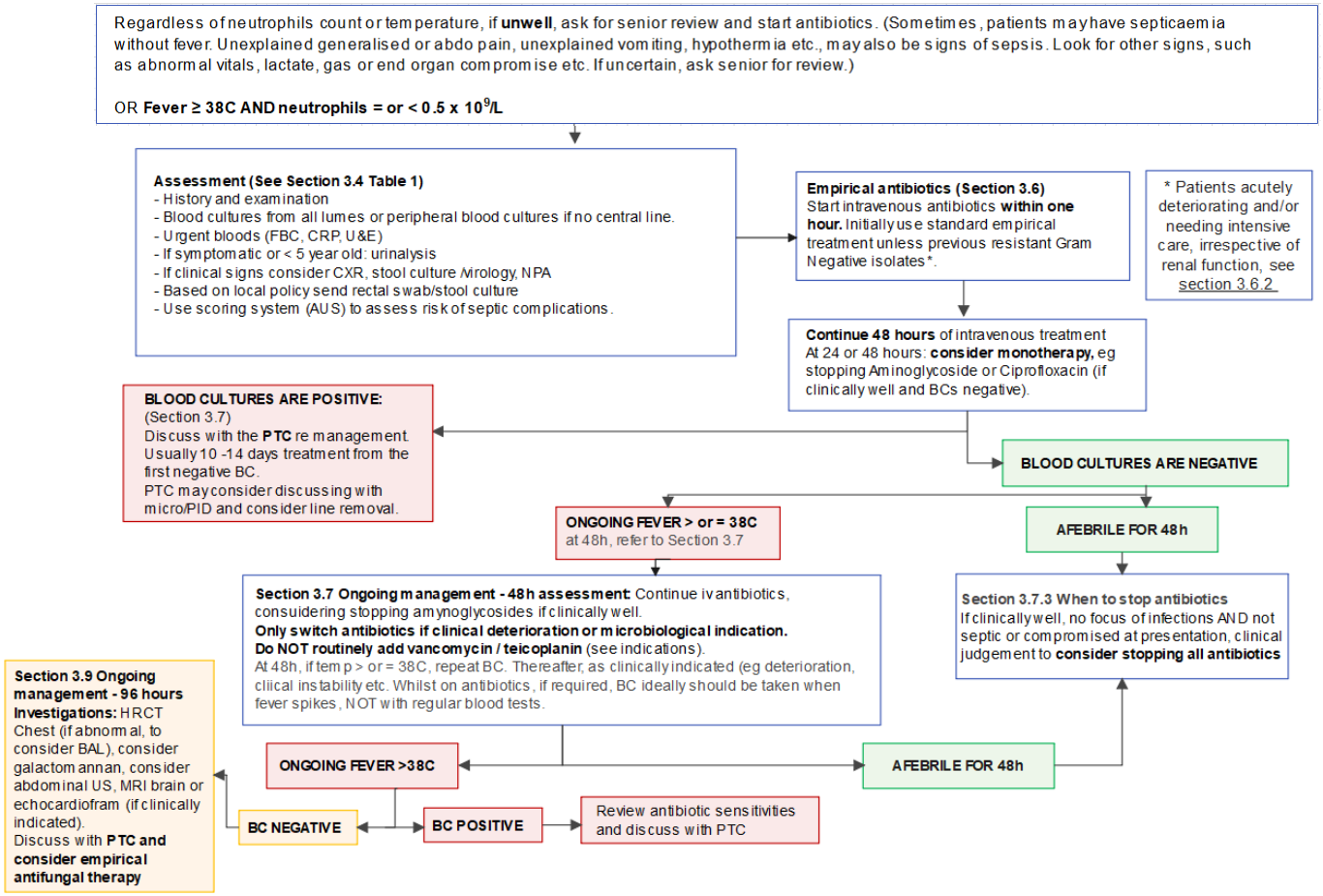
This document is designed to provide a brief background and practical application of a tiered, shortened, admission process. This protocol has been adapted from the paediatric low-risk FN program developed by Gabrielle Haeusler, National Centre for Infections in Cancer, Australia and in collaboration with Jess Morgan and Bob Phillips, University of York, and the CCLG team including Barry Pizer, Sujith Samarasinghe, Richard Grundy and Jessica Bate.

The protocol is not proposed to be a 'one size fits all' for all for PTCs and associated POSCUs. Instead it is recognised that centres should consider whether to adopt the full schema as written or to consider adapting the protocol according to their individual needs and particularly at this time, the effects of the COVID 19 pandemic on services.

Table 1, presents the Australian scoring system but also contains suggested variations to practice that centres may wish to consider for their own circumstances.

3.6 Febrile Neutropenia: Inpatient (IP) Pathway

Flow diagram / Summary of the emergency management – Inpatient Pathway



3.6.1. Empirical First-Line Antibiotics - to be administered within 1 hour

Assess as per Sections 3.3 and 3.4 above.

Standard first-line empirical antibiotics (Note **Section 3.6.2 Special Scenarios** below, if patient's first line antibiotics differs from piperacillin/tazobactam and aminoglycosides, this should be clearly documented in patient's medical records.)

ǂ Piperacillin / tazobactam 90mg/kg four times a day (max 4.5g)**
or as per local dose banding policy

AND

ǂ Aminoglycoside (check level prior to second dose)**:**
Gentamicin once daily* once daily (as per BNFc) or Amikacin (as per local policy)

UCLH (non-sarcoma, non-bone tumour) & GOSH: piperacillin/tazobactam and amikacin
RMH: piperacillin/tazobactam and gentamicin
POSCU: as per local policy & dependent on local microbiological resistance profile

For severe infections, follow local policy. ǂ These doses are from BNFc and BNF (Oct 2018). If future versions of BNFc/BNF change these to alternative doses, the authors recommend using new doses from newer versions of BNFc/BNF

- Alternative broad-spectrum antibiotics according to Trust local written policy, agreed with local microbiologists, considering local bacterial resistance patterns could be used instead of piperacillin / tazobactam and aminoglycosides (gentamicin or amikacin).
- Alternative to aminoglycosides (see **Section 3.6.2 Special Scenarios** below for further details):
    - **Oral ciprofloxacin** can be used (intravenous ciprofloxacin should only be used if clinical poor gastrointestinal absorption or used to treat confirmed Gram negative central venous catheter infection).
    - Oral ciprofloxacin dose for children: 20mg/kg twice daily (max. per dose 750mg for severe infections)
    - For UCH bone tumour and sarcoma patients, oral Ciprofloxacin 500 mg twice a day (or 750mg twice a day for severe infections) can be used to replace aminoglycosides. ie empirical treatment is Ciprofloxacin with Piperacillin/tazobactam – if endoprosthesis in situ, add **teicoplanin** - if signs of prosthetic infection e.g. increased pain, swelling or local temperature (see special scenario below)
    - **m.1555A>G variant (A1555G): Untested or patients with pending results: use standard antibiotics (ie piperacillin / tazobactam with aminoglycosides)** (See Section 3.6.2.10 for rationale). For the very small number of patients with known and confirmed mutation in m.1555A>G variant (A1555G). At the time of identification of confirmed mutation, GOSH clinical team to discuss with microbiologist to document antibiotic plan. If clinically non-septic, then avoid aminoglycosides (may consider using ciprofloxacin in place of aminoglycosides in a well and non-septic patient).

- ***It is recommended to stop aminoglycoside or ciprofloxacin (if used as dual antibiotic therapy) treatment early, i.e. at 24 or 48 hours from initiation of therapy, provided blood cultures are negative and if clinically appropriate.***
- Continue co-trimoxazole prophylaxis during febrile neutropenic episode.
- The empirical regimen is the same irrespective of previous antibiotic courses unless there are known antibiotic resistance guiding recommendations for an individual patient.
- **All Trusts should monitor resistance patterns including ESBL-producing bacteria & MRSA.**
- Initial monotherapy is **not** recommended for any patients even for those with neutrophils above 0.5 x 10^9/l in view of the frequency of piperacillin/tazobactam resistant organisms among PTC patients in London.

3.6.1.1 GOSH microbiology data and resistance patterns.

- **Antibiotic Resistance Data**: (Source: Dr Jim Hatcher, GOSH microbiologist. GOSH data over 5-year period from 2018 and 2022, positive blood culture isolates for all Pseudomonas and Enterobacterales species. *Excluding cultures from other PTC's or POSCU's*) showed:

Antibiotic	% resistance	Total isolates resistant	Total isolates tested
Ciprofloxacin	15.3%	46	301
Piperacillin/tazobactam	10.9%	31	284
Gentamicin	9.3%	28	300
Amikacin	2.6%	8	302
Meropenem	4.0%	12	301
Both Piperacillin/tazobactam and Ciprofloxacin	6.7%	20	300
Both Piperacillin/tazobactam and Gentamicin	5.0%	15	299
Both Ciprofloxacin and Gentamicin	5.7%	17	299
Both Ciprofloxacin and Amikacin	2.3%	84	3608
Both Piperacillin/tazobactam and Amikacin	1.7%	5	301
Both Meropenem & Amikacin	1.2%	43	3603

3.6.2. Special scenarios:

i. 3.6.2.1 Clinically unstable and deteriorating patients ♦ (new presentation of sepsis) needing Intensive Care (Irrespective of renal function)

- First choice: **Piperacillin/tazobactam with aminoglycosides§** ,
- Second choice: **Meropenem with aminoglycosides§** (consult microbiology before starting)

  Discuss with PTC consultant, microbiology and/or renal team for advice on appropriate antimicrobial therapy, which should include minimum of two broad spectrum intravenous antimicrobials covering Pseudomonas, Gram negative +/- Gram positive organisms as clinically appropriate.

♦ **Clinically unstable and deteriorating patients** are patients with evidence of respiratory distress, abnormal vital signs such as respiratory rate, oxygen saturation, heart rate, blood pressure, capillary refill time, altered neurological status or evidence of multi-organ failure. These patients require frequent medical reviews, frequent PTC updates and if appropriate prompt referral to intensive care retrieval services and Paediatric Intensive Care Units.

- It is crucial to review **previous microbiological isolates** and sensitivity/resistance profile at PTC (primary treatment centre) and local hospitals.

- If patient is acutely septic, clinically and/or cardiovascularly unstable (eg clinically still unstable after 40ml/kg fluid bolus, need for intensive care, intubation/ventilation and/or inotropic support), then Piperacillin/tazobactam with ciprofloxacin is **NOT** adequate, this combination should be avoided in acute septic deterioration. Hence first choice of **Piperacillin/tazobactam with aminoglycosides§**. If in doubt, discuss urgently with microbiologists.

§ **Aminoglycosides Renal Impairment Note:** if aminoglycosides are to be given and there is evidence of renal impairment, the dose will need to be appropriately reduced as per BNFc renal impairment guidance. The aminoglycoside could be prescribed as a single dose and review after 24 hours, alternatively it could be prescribed to be given regularly but with trough levels prior to each dose, hold subsequent doses and review each dose with levels ("trough and hold"), discuss with microbiology/renal team as needed.

Avoid delay: appropriate broad-spectrum antimicrobials must still be given within 1 hour of identification of Neutropenic Sepsis. (As per NICE guidelines on Sepsis: recognition, diagnosis and early management (Published: 13/7/2016 www.nice.org.uk/guidance/ng51).

For patients already on antimicrobials who develop acute clinical and/or cardiovascular deterioration, if there is clinical decision to change antimicrobials (especially if concerns with drug resistant organisms), then new antimicrobials should be administered within ONE HOUR of decision to change.

ii. 3.6.2.2 Patients (clinically stable) with renal impairment or at risk of renal impairment

- First choice: **Piperacillin/tazobactam +/- ciprofloxacin.**
- It is vital to monitor patient's clinical progress carefully and closely; if there is deterioration in clinical/cardiovascular status, acutely septic or deterioration needing intensive care: irrespective of renal function or risks of renal impairment (ie including "Patient groups at risk of renal impairment" below), aminoglycosides should be given as 1st line, or ciprofloxacin immediately changed to amikacin without delay. For details, see ICU section above (3.6.2.1) and data on resistances from section 3.6.1.1.

Patient groups at risk of renal impairment:

a. Patients receiving cisplatin (e.g. Hepatoblastoma, osteosarcoma, medulloblastoma)
b. Patients with a single kidney (e.g. Wilms post nephrectomy)
c. Renal tumours or genetic syndromes predisposing to renal tumours.
d. High risk neuroblastoma during induction chemotherapy
e. Infant ependymoma

Avoid aminoglycosides irrespective of renal function in "Patient groups at risk of renal impairment" as per above?

- In 4th edition v2.0 update, it was discussed whether the above group of patients, irrespective of renal function, should all avoid aminoglycosides in their first line neutropenic sepsis antibiotics by default. However, there is insufficient data to support this change of practice. Thus oncology team at GOSH is planning to audit practice and outcome of patients when aminoglycoside avoiding regimes (eg Piperacillin/ tazobactam and ciprofloxacin) is used irrespective of renal function.

iii. 3.6.2.3 Patients who are known to be colonised by resistant organisms

Empirical treatment in patients with known colonization should be started as per other patients. ie within 1 hour of presentation. In order to avoid any delay, for patients with known antibiotic resistance or colonization in whom first line empirical treatment differs from standard empirical treatment: it is recommended patients' medical records should be clearly documented with a personalised "first line intravenous antibiotics" plan, this plan need to be easily accessible to all staff in case of emergency presentation. If required, medical team should pre-discuss with microbiology.

In case of persistent fever and/or clinical deterioration, please discuss with microbiologist and consider adjusting the treatment for patients colonised with:

-MRSA: discuss with microbiology and consider early addition of **vancomycin**

-VRE: discuss with microbiology and consider addition of **linezolid**

-ESBLs: discuss with microbiology and consider early use of a **carbapenem** at presentation of fever.

-Piperacillin-tazobactam resistant Gram-negatives. Consult microbiology.

iv. 3.6.2.4 Bone prosthesis

If not acutely septic, empirical treatment is **ciprofloxacin with piperacillin/tazobactam**. If endoprosthesis in situ and showing signs of prosthetic infection (eg increased pain, swelling or local temperatures) add teicoplanin as 3rd antibiotic.

v. 3.6.2.5 Meningitis

If meningitis is suspected, use **meropenem** (meningeal doses) instead of piperacillin / tazobactam (as latter is not appropriate for CNS infections). Recommend to seek specialist advice from microbiology/infectious diseases.

vi. 3.6.2.6 VP (ventriculo-peritoneal) shunt

Consider shunt infection in patients presenting with fever and a VP shunt in situ. These patients must be discussed promptly with the PTC and neurosurgical team. **Meropenem and vancomycin** would be the empirical treatment of choice if there are symptoms/signs of shunt related infection and when other focal infections had been rule out.

vii. 3.6.2.7 Patient at risk of Gram-positive infection

Consider adding **teicoplanin or vancomycin** for penicillin allergic patients receiving ciprofloxacin and gentamicin who have significant mucositis to improve cover for Gram positive organisms. Vancomycin (or other agents active against aerobic Gram- positive cocci) should be considered for specific clinical indications, including:

1. Positive blood culture for Gram-positive bacteria, before final identification and susceptibility testing is available
2. Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
3. Skin or soft-tissue infection at any site
4. Colonization with methicillin-resistant Staphylococcus aureus
5. Haemodynamically unstable patient and suspected Gram-positive sepsis.

viii. 3.6.2.8 Allergies

Known allergy to beta-lactams, a suggestion for general first line antibiotics (though ideally plan should be discussed with microbiologist at diagnosis and base decision on local microbiological flora and patient's microbiological resistance profile): **ciprofloxacin plus amikacin +/- anti-Gram positive.** If no other alternative and ciprofloxacin plus gentamicin is the only option, then POSCUs must be extra vigilant, as deterioration on ciprofloxacin plus gentamicin may indicate antibiotic resistant sepsis. Important to note as per data above, 5.7% of Gram-negative blood cultures isolates at GOSH were resistant to ciprofloxacin plus gentamicin. Note antibiotic resistance profile in other PTCs and POSCUs is likely to be different.

ix. 3.6.2.9 Pneumocystis jirovecii pneumonia (PJP)

Consider PJP in a child with leukaemia or Hodgkin's disease who has missed co-trimoxazole prophylaxis

x. 3.6.2.10 m.1555A>G (a.k.a. A1555G)

GOSH patients only (m.1555A>G variant NOT routinely tested for UCLH or RMH patients)

Untested or patients with pending result for m.1555A>G:

Use standard first line empirical antibiotics (ie piperacillin / tazobactam with aminoglycosides) whilst result is pending. (ie this includes newly diagnosed cancer patients at POSCU or GOSH; as well as patients whose test had been sent, but results are pending).

Note: new GOSH policy re: m.1555A>G variant (A1555G). GOSH Drugs & Therapeutics Committee (DTC), Antimicrobial Stewardship (AMS) & haematology/oncology teams agreed that for patients without results for m.1555A>G variant (including untested newly diagnosed patients at POSCU or PTC; and patients whose m.1555A>G variant test result is still pending etc), ***such patients SHOULD receive aminoglycosides as part of their first line neutropenic sepsis antibiotics (ie same as standard 1st line piperacillin / tazobactam with aminoglycosides).*** This is because GOSH DTC, AMS & haematology/oncology teams all agreed the benefit of giving aminoglycosides outweigh the risk of avoiding.

- In one series, prevalence of m.1555A>G was reported as 1 in 520 (0.19%) (Bitner-Glindzicz et al 2009). An adult cohort from UK showed prevalence of 1 in 385 (0.26%) (Rahman et al 2012)
- GOSH is still testing new patients for m.1555A>G variant.

Patients with confirmed mutation in m.1555A>G variant

When confirmed mutation is identified, GOSH clinical team must discuss with microbiologists to carefully document antibiotic plan for both of following scenarios in GOSH and POSCU medical records:

- **Clinically well, stable and non-septic**
  Avoid aminoglycosides; may consider using ciprofloxacin in place of aminoglycosides in a well and non-septic patient (pre-confirm plan with microbiologists)
- **Acutely unwell, deteriorating and/or septic (eg metabolic acidosis, requiring fluid boluses and/or PICU etc)**
  For confirmed mutation in m.1555A>G variant, antibiotic plan for acute sepsis must be pre-discussed with microbiologists and clearly documented in medical records.

Drug doses and Therapeutic Drug Monitoring (TDM)

- Aminoglycosides and vancomycin require TDM monitoring (and teicoplanin for those units that are able to perform teicoplanin TDM)
- Antimicrobial doses and monitoring will be done as per BNFc (choose doses for severe infections) and local guidelines.
- We strongly recommend that POSCUs develop institutional guidelines in collaboration with the PTC, if still not available.

3.7 Ongoing management - 48 hours assessment - Inpatient Pathway - neutropenic sepsis:

Review all culture results regularly.

48 hours since onset of neutropenic sepsis, if temperature > or = 38°C, repeat blood cultures from all lumens. Thereafter as clinically indicated, eg deterioration, clinical instability etc. Whilst on antibiotics, cultures ideally should be taken when the fever spikes, NOT with the regular blood work. (Haeusler et al 2021)

Close monitoring of full blood count, electrolytes and TDM (eg aminoglycoside levels.)

3.7.1. Microbiological documented infection

- If cultures are positive, repeat blood cultures at 48 hours (to ensure clearance of bacteraemia) and review antibiotics as soon as sensitivities are available.
- All cases with positive blood cultures should be discussed with PTC.
- If a causative pathogen is identified, the patient should be treated with narrower-spectrum antibiotics, according to the causative organism identified.

Duration of intravenous antibiotic therapy (if in doubt, discuss with microbiology)

- Positive cultures always to be discussed with PTC and microbiology
- Positive blood cultures or bacteraemia due to catheter related infection: these patients usually need treatment for at least 10 days from first negative blood culture. Always discuss with local microbiology team and PTC.
- If Central Venous Catheter is removed for Central Line-Associated Bloodstream Infections (CLABSI), dependent on pathogen, duration of antibiotics may be shorter. Discuss with microbiology and PTC.
- If there is doubt about whether an infection is a true bacteraemia or a line infection only, take peripheral blood cultures in addition to cultures from the central venous access device.
- Well children with line infections caused by coagulase negative staphylococcus can often be managed at home with line locks or intravenous teicoplanin; it is important to check sensitivities (if in doubt, discuss with microbiology). Repeat blood cultures to ensure clearance of bacteraemia)
- Certain infections such as osteomyelitis, fungal infections and *Staphylococcus aureus* will require longer treatment. Discuss with microbiology team and PTC.
- If blood cultures are positive for the following organisms, they should **never** be treated as 'contamination': Gram negative organisms including *Pseudomonas aeruginosa*,

Enterobacteriaceae (eg *E coli, Klebsiella spp Enterobacter spp*), *Staphylococcus aureus*, fungus (*Candida* etc)

3.7.2. When to remove the Central Venous Catheters (CVC)?

No routine removal of central venous access device (unless clinically or microbiologically indicated). If cases of positive blood cultures for *Staphylococcus aureus*[**], *Pseudomonas species*, fungi, mycobacteria, or recurrent blood cultures positive for the same organism, catheter removal should be considered and urgently discussed with PTC.

[**]Clinical team need to understand difference between *Staphylococcus aureus* (higher risk infection, which may disseminate to organs and/or CVC line infection) and single blood culture positive for *Coagulase Negative Staphylococcus* (CONS) which may cause CVC line infection, but rarely disseminate.

3.7.3. When to change antibiotics?

Modifications to the initial antibiotic regimen should be guided by clinical and microbiologic data

- Only consider switching antibiotics if **clinical deterioration** or **microbiological indication.** If clinical deterioration, escalate the initial empirical coverage to include Gram-negative, Gram-positive and anaerobic bacteria.
- Even if patient continues to be febrile, consider whether aminoglycoside or fluoroquinolones can be safely discontinued at 24-48 hours if patient clinically stable and blood cultures are negative.
- No routine addition of vancomycin or teicoplanin if unresponsive fever.
- **Vancomycin or teicoplanin** should only be added if microbiological indication or local signs of infection from central venous access device or endoprosthesis.
- For patients with an endoprosthesis, if clinically well at 48 hours, no positive cultures, and no clinical suspicion of endoprosthesis infection (local pain, swelling, etc), teicoplanin should be discontinued if it was empirically started.

3.7.4. When to stop iv antibiotics?

Before stopping antibiotics, ensure risk assessment complete and appropriate.

At any stage at or after 48 hours assessment, all antibiotics may be stopped if:

- Patient afebrile (<38.0ºC) for 48hrs
- All blood cultures are negative **AND** no clinical focus of infection
- Patient is clinically well **AND** patient was not clinical septic/compromised at presentation
- Clinical judgement that patient is safe to stop antibiotics

The de-escalation strategy may be considered even before haematological recovery.

3.7.5. When to change to oral antibiotics?

For patients with fever of unknown origin consider switching to oral antibiotics those patients at **low risk**, stable condition, and negative blood cultures prior to discharge home/parent-led care. This can happen after a period of iv treatment (based on the initial risk stratification).

Oral antibiotics might happen assuming no mucositis, no vomiting, no significant diarrhoea suggesting reduced absorption.

The suggested antibiotic regimen is a combination of oral ciprofloxacin Plus oral co-amoxiclav. If allergic to penicillin, consider clarithromycin instead.

3.8 Discharge – Inpatient Pathway

- Patients may usually be discharged immediately after stopping antibiotics.
- Inform parents to return should the child become febrile again or unwell.
- Please, refer to the **Section 3.5 CCLG FN pathway**, for discharge considerations.

3.9 Ongoing management (Inpatient Pathway) - after 96 hours intravenous antibiotic treatment if persistent fever

All patients who are febrile and neutropenic at 96 hours should be discussed with the PTC, and from then onwards, on a daily basis.

Only consider switching antibiotics if clinical deterioration or microbiological indication.

Even if patient continues to be febrile, consider whether aminoglycoside can be safely discontinued if patient clinically stable and blood cultures negative if not stopped earlier.

3.9.1 Invasive Fungal Diseases (IFD).

3.9.1.1. Risk factors for IFD

- Host dependent factors: whereas low risk for IFD, does not mean complete lack of risk, there are patients whose risk of infection is significantly higher.

Risk	**Patient population**
High risk (close to and > 10%)	- Acute Myeloblastic leukaemia (AML) - Relapse acute leukaemia - Allogeneic haematopoietic stem cell transplantation (until engraftment) or GvHD) - High risk acute lymphoblastic leukaemia
Low risk (close to and < 5 %)	- Acute lymphoblastic leukaemia - Non-Hodgkin's lymphoma - Autologous haematopoietic stem cell transplantation
Sporadic	- Paediatric solid tumours - Brain tumours - Hodgkin's lymphoma

- The principal risk factors for development of IFDs in paediatric cancer/HCT patients are similar to those in adults and include prolonged and profound granulocytopaenia (absolute neutrophil count (ANC) of ≤500/uL / $0.5x10^9$/L for ≥ 10 days), the use of glucocorticosteroids in pharmacological doses (≥0.3 mg/kg/day prednisone or equivalent), mucosal tissue damage; and, limited to invasive candidiasis, TPN and/or use of broad-spectrum antibacterial agents (especially for prolonged periods) and the presence of central venous catheters.

3.9.1.2. Investigations:

Mandatory investigations

- Early chest HR-CT
- Abdominal US

Investigations to consider:

- BAL (in patients with findings at the chest HR-CT).
- Serum and/or BAL fungal diagnostics as per local policy (Groll et al 2021)
- MRI or CT brain with contrast
- MRI or CT sinuses
- Echocardiogram
- Fundoscopy

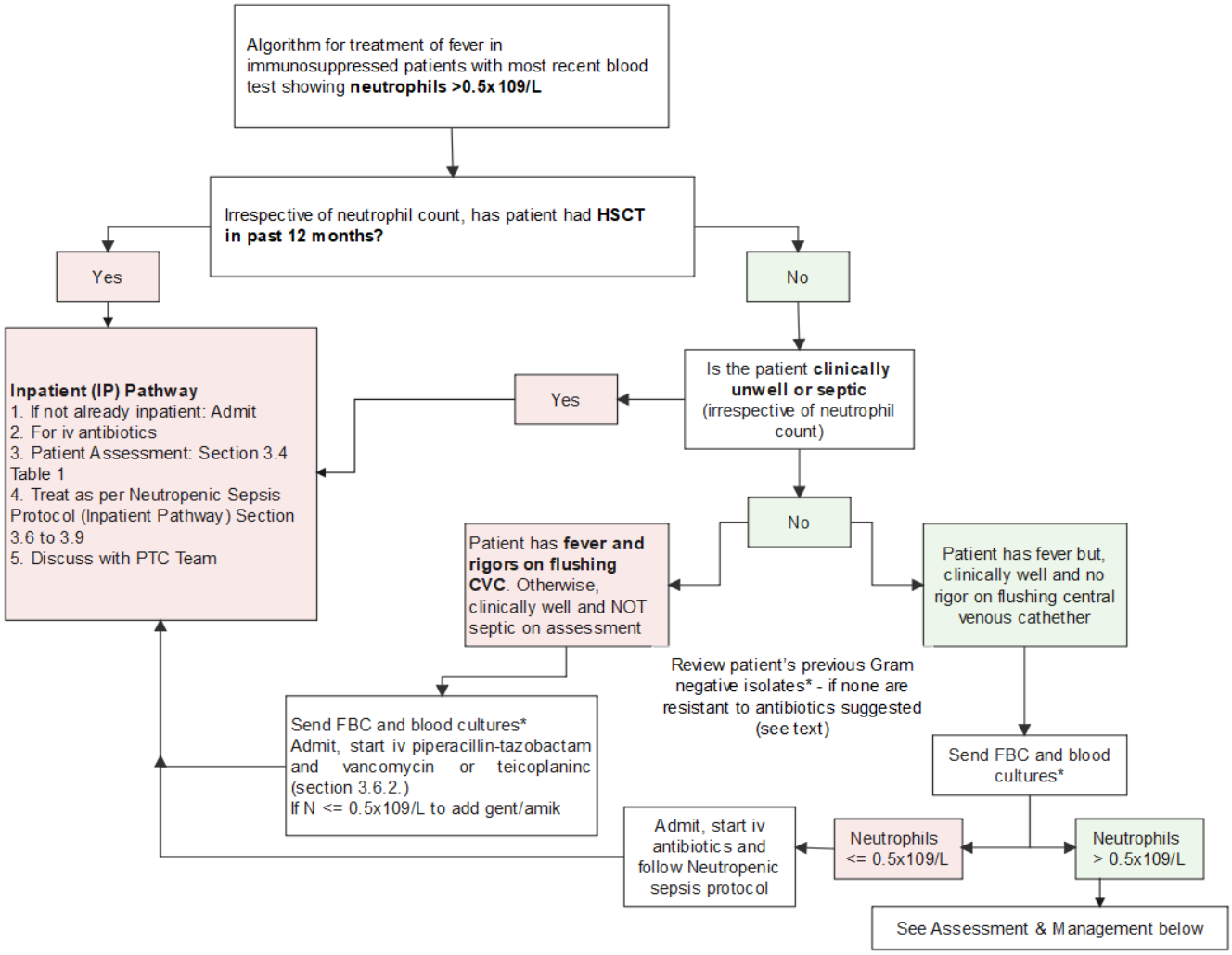
3.9.1.3. Antifungal use

- Start empirical antifungal treatment for GOSH/RMH patients after 96h of fever with no response to standard antibiotics.
- For UCLH patients, always discuss with UCLH before commencing antifungals.
- In **low-risk patients**, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy can be deferred to 6-7 days of fever and should be discussed with PTC .
- Empirical antifungal use (order below is NOT indicative of preference or priority):
  - **Liposomal amphotericin B (Ambisome) 3 mg/kg once a day or**
  - **Echinocandins (Micafungin or Caspofungin)**
- Useful reference ECIL-8 (Groll et al 2021)
- Continue until antifungal therapy resolution of fever, lack of evidence of fungal infection on radiology, improving clinical signs and rising neutrophil count, (usually 24 hours after stopping antibacterials and patient can then be discharged)

3.9.1.4. Patients with persistent fever (> 7 days)

- Discuss with PTC

3.10 Febrile non-neutropenia



Assessment and management of febrile non-neutropenia

Non-neutropenic patients with fever do not all need to receive antibiotics routinely, but each case should be assessed individually and treated according to clinical findings.

Assess each patient carefully and treated as per clinical findings, including:

-Standard clinical examination
-Central venous catheters (exit site, tunnel infection, cellulitis)
-Shunts
-Endoprosthesis in situ
-Blood tests: FBC and blood culture from each lumen of CVL (as a minimum)
-**AUS score**

- If ventriculo-peritoneal shunt or endoprosthesis infection is suspected, ensure discussion with the PTC and the patient's lead neurosurgeon or orthopaedic surgeon respectively. Do not aspirate without discussion with PTC & the surgeons.
- Central venous access devices can harbour organisms that on flushing lead to bacteraemia. Coagulase negative staphylococci are the typical responsible organism, but it is vital not to miss

streptococcal or gram-negative infections. Fever and rigor within hours of flushing are the classical symptoms of line infection, but other more non-specific symptoms such as vomiting and abdominal pain without fever are also described. Thus, any patient who is unwell within 8 hours of line flush should receive immediate standard dual therapy as above. Early discussion with the PTC and consideration of line removal is mandatory.

- For central venous access device exit site or tunnel infections, treat with glycopeptides (teicoplanin/vancomycin) after taking blood cultures and/or skin swabs (flucloxacillin in confirmed MSSA infections).

After thorough assessment as per above, management options include:

1. If lack of clinical indications, consider no antibiotics
2. **Consider oral antibiotics (co-amoxiclav and ciprofloxacin) as per Section 3.5 CCLG FN pathway.**
3. If positive blood cultures, refer to and manage as per Section 3.7.1. Microbiological documented infection.

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4.

PREVENTION AND TREATMENT OF SPECIFIC INFECTIONS AND VACCINATIONS IN PATIENTS WHO HAVE RECEIVED CHEMOTHERAPY OR HAEMATOPOIETIC STEM CELL TRANSPLANT (HSCT)

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4. Prevention and Treatment of Specific Infections and Vaccinations in Patients who have Received Chemotherapy or Haematopoietic Stem Cell Transplant (HSCT)

4.1 Varicella-Zoster

Varicella zoster virus (VZV) is a human alphaherpesvirus, which causes varicella (chicken pox) as the primary infection; VZV then establishes latency and re-activates to cause herpes zoster (shingles).

Varicella can be life threatening in children with cancer, and infection is associated with cancer treatment delays. Ask about a history of clinical varicella in the patient and household contacts at diagnosis and arrange vaccination of household contacts with a negative history of chickenpox (see below). **Pre-transfusion VZV antibody status should be checked on all patients at the time of diagnosis** and should be recorded in the parent held record.

The majority of children with cancer are treated with standard-dose chemotherapy but some children require high dose chemotherapy +/- radiotherapy followed by haematopoietic stem cell transplant (HSCT). Special circumstances occur after autologous or allogeneic HSCT where the child should be considered at risk irrespective of VZV antibody status until at least 2 years post HSCT and at least 12 months off all immunosuppressive therapy. Post-exposure prophylaxis should be guided by the PTC for these patients as there is variation in practice.

Prevention of VZV

4.1.1 Vaccination of siblings/household contacts

Exposure within the household is the setting most likely to cause varicella in the immunocompromised child. It is recommended that healthy susceptible close household contacts of immunocompromised patients receive the VZV vaccine; household contacts that are over one year of age and without clinical history of chicken pox should be vaccinated (they do not require serological testing prior to this). The small risk of vaccine related varicella (usually within 1 month of vaccination) should be discussed with the patient and parents. If vaccine related varicella does occur in the vaccine recipient, follow the guideline below for significant exposure.

4.1.2 VZV Post-exposure prophylaxis (PEP)

Patients receiving standard-dose chemotherapy and up to 6 months after receiving standard-dose chemotherapy and following HSCT are at risk of developing varicella following a significant VZV exposure and should be considered for post-exposure prophylaxis

4.1.3 Definition of significant exposure to VZV

Three aspects of exposure to VZV during the infectious period are relevant when considering the need for post-exposure prophylaxis for a susceptible individual:

1. Type of VZV infection in the index case:
    a. Chicken pox infection
    b. Disseminated shingles
    c. Immunocompetent individual with exposed shingles lesions (eg ophthalmic)

d. Immunosuppressed patients with localised shingles on any part of the body (in whom viral shedding can be greater).

2. The timing of the exposure:
    a. Varicella or disseminated zoster - between 24 hrs before onset of rash until no new lesions cropping/ crusting of lesions (usually 5 days but may be longer in immunosuppressed individuals)
    b. Localised zoster – day of onset of rash until crusting of lesions

3. Closeness and duration of contact:
    a. contacts where there is continuous exposure (eg household contacts)
    b. contacts where there have been multiple exposures during the infectious period (eg family friend visiting on more than one occasion)
    c. contacts with a single exposure to a case of chicken pox in the infectious period in the same small room (eg house, classroom, 2-4 bed hospital bay) for a significant period of time (>15 minutes)
    d. face to face contact eg having a conversation
    e. immunosuppressed contacts on large open wards

4.1.4 Special circumstances which may increase risk of VZV infection

Special circumstances may increase the risk of the child getting VZV infection or getting more severe disease (even despite post-exposure prophylaxis).
This can relate to:

1. prolonged & continuous household exposure / contact, e.g. to sibling etc. It is worth considering if there is any possibility of separating and removing the patient from the "contact" / index case and household. Furthermore, it is important to take additional history regarding other non-VZV immune household family members (e.g. other siblings, cousins living in same household etc.), these non-immune family members could subsequently develop VZV; thereby prolong continuous VZV exposure further. i.e. adding more weight in consideration of removing patient from household (if logistically possible). Remember that if family is unable to separate the patient and the household index case, then the patient's "last day of exposure" to VZV should be considered as the day when household index case's lesions are all crusted and no new crops. This need to be considered in the timing and duration of post-exposure prophylaxis for both aciclovir and VZIG.
2. high risk periods during treatment – e.g. high dose steroids for 7 days or greater (e.g. during ALL induction, delayed intensification or relapse ALL re-induction etc)

There is no literature or data to confirm the above nor are there published guidelines on management of these circumstances, therefore concerns about additional risk should be discussed with PTC on an individual basis.

4.1.5 Rationale for guideline

Chickenpox (varicella) infection in immunosuppressed children can result in severe and even life-threatening varicella disease. PEP is recommended to attenuate disease and reduce the risk of complications in these at-risk individuals.

There is now evidence that some children who were VZV IgG positive at diagnosis, may lose this immunity during chemotherapy treatment. This relates particularly to children receiving treatment for haematological malignancies and until at least six months of completion of immunosuppressive chemotherapy and to patients who have received a haematopoietic stem cell transplant. In order to simplify this guideline, we have not differentiated between the type of malignancy being treated for the

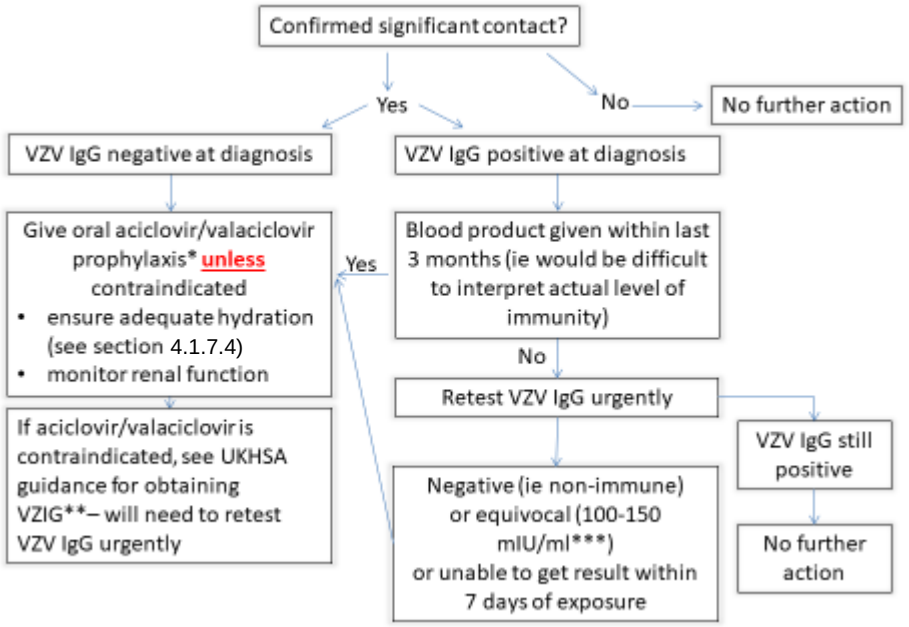
management of chicken pox contact. Therefore, following significant chicken pox exposure, these children should have VZV antibodies retested urgently in order to see if they still have a positive VZV IgG.

Children who were VZV IgG negative at diagnosis, are less likely to develop significant protective immunity during immunosuppressive treatment. Therefore, it is recommended that post-exposure prophylaxis is given to this group without retesting their antibodies.

See the detailed UK Health Security Agency (UKHSA) guide below 'Guidelines on post exposure prophylaxis (PEP) for varicella and shingles (April 2022)'[1] for the latest information. VZIG may still be obtained for children where aciclovir is contraindicated.

Post exposure prophylaxis for chickenpox and shingles - GOV.UK (www.gov.uk)

4.1.6 Figure 1: Management of patients with malignant disease until at least six months after completion of standard-dose chemotherapy or radiotherapy



* See section 4.1.7 for timing/dose of oral aciclovir/valaciclovir and supportive care.

** VZIG is issued by the Rabies and Immunoglobulin Service, Health Security Agency, Colindale (tel: 0330 128 1020), and some local UK HSA laboratories, following a risk assessment of the exposed individual.

*** Where laboratories provide the titre.

For patients who have had high-dose chemotherapy +/- radiotherapy followed by an autologous or allogenic HSCT, post-exposure prophylaxis should be guided by the PTC as there is variation in practice. Please contact the PTC for patient-specific advice.

For all other patients with malignant disease, until at least 6 months after receiving standard–dose immunosuppressive chemotherapy or radiotherapy, management is as per the flow diagram above (Figure 1).

4.1.7 Choice of VZV prophylaxis (Oral aciclovir or oral valaciclovir)

Oral Aciclovir / Oral valaciclovir:

4.1.7.1 ***Start day 7 post VZV exposure and continue until day 21.*** (The most critical period when oral aciclovir/valaciclovir is the most effective in preventing clinical VZV is likely to be between day 7 and 14 post exposure. Though authors of these guidelines strongly recommend to continue till day 21 following extensive review of the current available evidence)

4.1.7.2 ***This could be extended to day 28 post exposure if there are special circumstances*** (eg prolonged contact or high-risk treatment – see section 4.4 above).

4.1.7.3 If not concerned with compliance and in cases of special circumstances as per section 4.4 above, aciclovir/valaciclovir can be started from the day of knowledge of contact and continue up till day 21. (Or day 28 post exposure as per 4.1.7.2) The key period remains between day 7 until day 14. If the patient is able to tolerate a longer duration, then the risk of clinical VZV may be reduced further when given as longer duration.

Guide to time of presentation and length of treatment for patients with malignant disease, until at least 6 months after receiving standard–dose immunosuppressive chemotherapy or radiotherapy

	Patient presents prior to D7 (Day 7) post exposure to chicken pox	**Patient presents between D8 and D21 post exposure to chicken pox**
Standard exposure	Start PEP (aciclovir/ valaciclovir) from D7 until D21 post exposure	Discuss with PTC Start PEP and continue until at least D21 post exposure (or up to D28 depending on risk assessment)
'Special circumstances' as per section 4.4 E.g. prolonged/continuous household exposure (e.g. siblings, cousins, or others living in same household) or high-risk periods during treatment (eg ALL induction)	Discuss with PTC In cases of prolonged/continuous household exposure:- Start of PEP: from Day 6 (or earlier as directed by PTC) of index case's onset of rash (index case is infectious 24hr prior to rash onset) Last day of PEP: continued till i) 21 days from patient separating from index case into different households (if possible) or ii) If unable to separate, at least 26 days from index case's onset of rash (index case considered infectious till day 5 from onset) iii) or if index case is still infectious post day 5, PEP to stop 21 days from last day of "no new lesions and all lesions crusted" in index case (i.e. no longer infectious) Start PEP from D7 and consider giving until D28 post exposure	Discuss with PTC Start PEP and continue until at least D28 post exposure depending on risk assessment

Guide to Doses for PEP (please always check updated BNFc)

	Oral Aciclovir* (Dose as per UKHSA April 2022[1])	**Oral Valaciclovir** (Dose as per UKHSA April 2022[1])
Infants over 4 weeks to Children under 2 years age	10mg/kg 4 times daily	Not recommended
Children 2 to 17 years of age	10mg/kg (up to maximum 800mg), 4 times daily	20mg/kg (up to maximum 1000mg), 3 times daily

Use with caution if concern about renal impairment and maintain adequate hydration.

4.1.7.4 Supportive care for oral aciclovir/valaciclovir for VZV PEP

- Ensure parents aware the need to encourage oral fluid intake, ideally aim for at latest 100% maintenance volume orally.
- 2 times per week U&E whilst on VZV PEP (renal function only. Routine LFT's not indicated)
- Discuss with PTC if renal function deteriorates

4.1.8 VZIG and contraindication to aciclovir/valaciclovir

For individuals where oral antivirals are contraindicated, eg with renal impairment or intestinal malabsorption, VZIG may be considered (UKHSA April 2022[1]).

The following national guidance gives information about how to obtain VZIG and dosage.
Post exposure prophylaxis for chickenpox and shingles - GOV.UK (www.gov.uk) [1]

Administration of VZIG for prophylaxis (by slow intramuscular injection):

When a large-volume injection such as VZIG is to be given, it should be administered deep into a large muscle mass. If more than 3ml is to be given to young children and infants, or more than 5ml to older children and adults, the immunoglobulin should be divided into smaller amounts and given into different sites. The upper outer quadrant of the buttock can be used for the VZIG injection.

VZIG should ideally be administered within 7 days of the day of exposure. If a second contact is reported beyond 7 days of the first exposure, then repeat assessment based on the date of the second exposure should be made to determine the need for, and benefit from additional PEP.

Individuals for whom intramuscular injections are contraindicated, eg with bleeding disorders, should be given intravenous human normal immunoglobulin (IVIG) at a dose of 0.2g per kg body weight (i.e. 4ml/kg for a 5% solution) instead. This will produce serum VZV antibody levels equivalent to those achieved with VZIG. IVIG should ideally be administered within 7 days of the first contact.

4.1.9 Post autologous or allogenic HCST patients

Haematopoietic stem cell transplant patients are at risk of VZV irrespective of antibody status (ie no need to re-check VZV IgG at time of exposure) until at least 24 months post-transplant and at least 12 months off all immunosuppressive therapy. However, guidance on their management varies between PTCs and depends on whether they are already on prophylactic aciclovir or receiving regular IVIG. Please check the individual patient-specific guidance or with the PTC.

4.1.9.1 Individuals receiving regular IVIG replacement therapy do not require prophylaxis if the most recent dose was administered ≤ 3 weeks before exposure. Please discuss with the PTC.

4.1.9.2 Individuals on long term aciclovir/ valaciclovir prophylaxis e.g. post-haematopoietic stem cell transplant. If the dose of aciclovir / valaciclovir is lower than that stated in the UKHSA guidance[1] for PEP, then they will require their dose of aciclovir / valaciclovir to be temporarily increased to the PEP dose from the day of knowledge of contact (ideally by day 7 post contact) until day 21 following exposure to chicken pox. For patients within 12 months of a stem cell transplant, VZIG should also be considered. Discuss with the PTC.

4.1.10 Risk assessment following second exposure to chicken pox or shingles

Children re-exposed to varicella or zoster (see above for details of significant exposure) following post-exposure prophylaxis require a new risk assessment if a second exposure occurs:

- immediately following aciclovir prophylaxis
- within 3 weeks of VZIG or IVIG, no further prophylaxis is required
- between 3- and 6-weeks following administration of VZIG or IVIG, a further dose of VZIG should be administered without further testing
- more than 6 weeks following administration of VZIG or IVIG, retesting of a new sample is required
- if high risk circumstances, discuss individual case with PTC.

4.1.11 Information to parents after aciclovir / valaciclovir prophylaxis or VZIG

Even with aciclovir/valaciclovir prophylaxis or VZIG, children can still develop varicella. Lesions can be atypical – have a high index of suspicion.
After aciclovir prophylaxis or VZIG, the incubation period of varicella can be prolonged to 28 days.
If the child develops varicella, he/she will need admission for IV aciclovir.
Live vaccines are not to be given within 3 months of VZIG administration.

4.1.12 Treatment of Clinical Varicella/ Herpes Zoster

Varicella and herpes zoster can be fatal in immunosuppressed patients. Presentation may be atypical. Patients must be admitted for iv aciclovir for at least 5 days (or until there are no new lesions developing) followed by 5 days of oral aciclovir (check renal function and modify dose if needed). If cropping of new lesions continues the IV aciclovir should be given until no lesions develop and crusting of lesions occurs. Complete a total course of 10 days of aciclovir.

For doses see BNFc.

4.1.13 Supportive care with intravenous (IV) aciclovir

There is a significant risk of acute kidney injury with iv aciclovir, particularly with co-existing risk factors such as use of other nephrotoxic drugs or underlying co-morbidities. To minimise this, ensure adequate hydration with maintenance iv fluids and dose adjustment for renal impairment. Careful daily medical review as per below.

- 100% IV maintenance fluids with oral intake in addition as minimum
- Subsequently increase or reduce iv fluids as per clinical status and renal function.
- attention to strict fluid balance and avoid fluid overload
- Daily U&E (renal function only. Routine LFT's not indicated)
- Avoid other nephrotoxic drugs where possible
- If febrile, start antimicrobials as per Supportive Care Protocol. Discuss with the PTC re stopping nephrotoxic antimicrobials at the earliest opportunity based on the availability of culture results.

4.2 Herpes Simplex Virus

Oral herpes simplex virus (HSV) usually causes a mild, self-limiting infection of the lips, cheeks, or nose (herpes labialis or 'cold sores') or oropharyngeal mucosa (gingivostomatitis).

- Symptomatic primary infection usually presents as gingivostomatitis in children.
- HSV is usually transmitted via direct contact with infected secretions entering via the skin or mucous membranes, from a person who is actively shedding the virus.
- HSV infection can cause severe or life-threatening complications, particularly in immunocompromised people, including eczema herpeticum, eye disease including corneal ulceration, erythema multiforme, pneumonia, and encephalitis.
- Primary herpes labialis lesions usually resolve within 10–14 days; gingivostomatitis usually resolves within 2–3 weeks.
    - Herpes labialis may present with a prodrome of fever, sore throat, and lymphadenopathy, particularly in primary infections.
    - Initial symptoms of pain, burning, tingling, and itching may precede visible lesions and typically last 6–48 hours.
    - Herpes labialis lesions are typically crops of vesicles that rupture, ulcer, crust, and heal (usually without scarring).
    - Herpes gingivostomatitis lesions are typically crops of painful vesicles that rupture and form ulcers on the pharyngeal and oral mucosa.
    - People who are immunocompromised may have severe, atypical lesions anywhere in the oral cavity. This can be difficult to differentiate from mucositis and thus worth taking a viral swab.
    - Consider HSV in patients who present with oral mucositis but have not had significant doses of agents that are known to cause mucositis.

Management of patients with suspected oral herpes simplex

- Viral swab for HSV PCR
- If patient is clinically well and can drink, they may be treated with oral aciclovir or valaciclovir (doses as per BNFc 'Herpes simplex, treatment in immunocompromised or if absorption impaired')
- Hospital admission for iv aciclovir with iv fluids if the child is unwell, unable to swallow or is dehydrated (see section above on supportive care with iv aciclovir, dose as per BNFc 'Herpes simplex, treatment, in immunocompromised or in simplex encephalitis'). Maintain extreme caution re renal impairment as these children will often be dehydrated on admission. Always start iv fluids with iv aciclovir and monitor strict fluid balance.
- Analgesia to treat pain, may require a NCA or PCA if unable to swallow
- Seek specialist advice from the PTC if concern about complications of HSV are suspected
- Topical antiviral treatment is not recommended as unnecessary with oral or iv antiviral treatment
- If febrile, start antimicrobials as per Supportive Care Protocol. Discuss with the PTC re stopping nephrotoxic antimicrobials at the earliest opportunity based on the availability of culture results.

- Length of treatment for simple oral herpes simplex infection:
  5 days of iv aciclovir or oral aciclovir/valaciclovir (or longer up to 10 days if not initially improving).

4.3 Measles

Take an immunisation history from all newly diagnosed patients and their siblings/household contacts. It is helpful to document the measles IgG prior to starting treatment (before blood products are given).

Prevention of Measles Infection

Vaccination
The majority, but not all children, will have received measles vaccine as part of the universal childhood vaccination programme before their diagnosis of cancer. Measles vaccine is contraindicated in immunosuppressed patients and must not be given to patients once a cancer diagnosis is made and until at least 6 months after completion of chemotherapy or longer post HSCT (see below). Siblings/household contacts may receive the MMR vaccine as vaccine-acquired infection cannot be transmitted.

Post exposure prophylaxis
The need for intervention following measles exposure depends on the vaccination/ past measles infection status of patient and the degree of immunosuppression of the patient. The most immunosuppressed children may require urgent measles IgG testing and /or IVIG (i.e. those undergoing HSCT and until at least 12 months after finishing all immunosuppression and patients on treatment for ALL within and until at least six months after completion of immunosuppressive therapy).

For risk group classification, rationale and treatment using IVIG, refer to:

Guidelines on Post-Exposure Prophylaxis for measles June 2019 (publishing.service.gov.uk) [2]
or refer to subsequent and more up to date versions.

4.4 PJP - Pneumocystis Pneumonia (Formerly known as *Pneumocystis carinii PCP*) and other interstitial pneumonia

Causes of interstitial pneumonia in the immunocompromised patient may include *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii or PCP*), cytomegalovirus, measles, varicella-zoster fungal infections mycoplasma, legionella. Common respiratory viruses including influenza, parainfluenza, adenovirus and RSV, SARS-CoV-2.

Prevention of pneumocystis pneumonia (PJP) caused by *P. jirovecii*

Co-trimoxazole (trimethoprim/sulfamethoxazole) prophylaxis is given to all children on ALL chemotherapy according to protocol and to certain intensive solid tumour regimens (e.g. MMT 98, high risk neuroblastoma) or relapsed solid tumour protocols (e.g. Wilms', Group C).

For patients who cannot tolerate co-trimoxazole e.g., excessive myelosuppression during ALL therapy, PJP prophylaxis should continue with one of the alternative drugs. Data from patients living with HIV suggests that dapsone is a more effective choice than nebulised pentamidine or atovaquone. **G6PD qualitative assay should be performed before starting dapsone therapy.** For patients who cannot tolerate dapsone, nebulised pentamidine or oral atovaquone is recommended.

Diagnosis and management of clinical PJP

Clues are cough, fever, tachypnoea, lymphopenia, hypoxia, absence of chest signs on auscultation and bilateral infiltration on chest x-ray. Although unlikely in patients on prophylactic co-trimoxazole, it should be considered in patients with this clinical presentation. It is important to start treatment early at the first suspicion of PJP – discuss early with PTC.

Investigations (aimed at diagnosing PJP and other causes of interstitial pneumonia): -

- Routine culture of respiratory material for bacteria, mycobacteria and fungi
- Respiratory viral PCR (nose/throat swab or nasopharyngeal aspirate) – including mycoplasma, adenovirus, CMV
- Nasopharyngeal aspirate for *P. jirovecii* PCR
- PCRs on blood for CMV, EBV, adenovirus
- VZV serology and/or PCR if clinical suspicion or epidemiological association
- Legionella urinary antigen
- Serum (1,3)-Beta-D-Glucan concentration (non-specific fungal biomarker, but may be highly raised in PJP and also has a high negative predictive value for fungal infection)
- Serum galactomannan concentration (Aspergillus-specific fungal biomarker)
- Discuss with PTC – may require bronchio-alveolar lavage (BAL) for definitive diagnosis or exclusion of PJP

If there is a high level of suspicion for PJP or there is confirmed PJP infection, please discuss with the PTC for early transfer and for specific advice regarding treatment. Patients with respiratory compromise may need mechanical ventilation and/or admission to PICU.

First line therapy for suspected/confirmed PJP is high dose co-trimoxazole, often with erythromycin or clarithromycin (to cover the possibility of other atypical pneumonia pathogens while waiting for the definitive diagnosis). If no response at 24-48 hours discuss again with PTC for transfer/advice and consider addition of further antifungal/antiviral cover if not already started. Pentamidine is effective in most non-responders. Steroids may be life-saving in this situation - to be discussed on an individual basis (will need MDT discussion about risk/benefit)[3].

Useful reference: Pneumocystis jirovecii pneumonia - Treatment algorithm | BMJ Best Practice

4.5 Prevention of Infection and vaccination policies in Haematopoietic Stem Cell Transplant Recipients

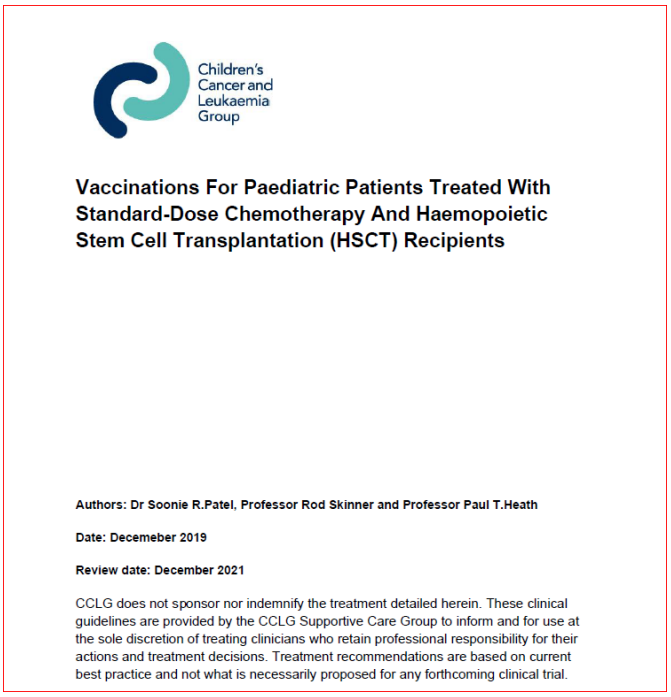
To avoid duplication of policies, please refer to individual PTC BMT unit's policy.

4.6 Vaccinations for Paediatric Patients treated with Standard-Dose Chemotherapy

To avoid duplication of policies, please refer to the most up to date version of:

Children's Cancer and Leukaemia Group: Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy And Haemopoietic Stem Cell Transplantation (HSCT) Recipients (Authors: Dr Soonie R.Patel, Professor Rod Skinner and Professor Paul T.Heath).

https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/CCLG_Vaccination_Guidelines_Jan_2020.pdf [Last read 10/3/2023]


Children's Cancer and Leukaemia Group

Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy And Haemopoietic Stem Cell Transplantation (HSCT) Recipients

Authors: Dr Soonie R.Patel, Professor Rod Skinner and Professor Paul T.Heath

Date: Decemeber 2019

Review date: December 2021

CCLG does not sponsor nor indemnify the treatment detailed herein. These clinical guidelines are provided by the CCLG Supportive Care Group to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.

Or refer to subsequent and more up to date versions.

References

1. UK Health Security Agency (UKHSA) guide below 'Guidelines on post exposure prophylaxis (PEP) for varicella and shingles (April 2022)

2. Public Health England Guidelines on Post-Exposure Prophylaxis for measles (June 2019)

3. Pneumocystis jirovecii pneumonia - Treatment algorithm | BMJ Best Practice

5.

5. DRUGS USED IN THE TREATMENT OF INFECTIONS (Removed)

Refer to **https://bnfc.nice.org.uk/** or local guidelines/policies

To avoid duplication of doses between this SCP with BNFc and BNF, Chapter 5 and majority of drug doses have been removed from SCP 4th edition v2.0 (and subsequent editions). This is due to electronic BNFc and BNF could be updated on monthly basis, therefore it is unrealistic for guidelines such as this SCP to keep up to date at the same rate. When there was discrepancy between updated BNFc doses and SCP in the past, this had led to confusion in clinical teams.

The drug doses retained in this SCP are as follows:

1) Doses not found in BNFc
2) Differ than those found in BNFc
3) Emergency drugs included for convenience. However the readers need to be aware that if BNFc or BNF do change doses for these emergency drugs, then the authors recommend the readers to follow the new and updated doses in BNFc or BNF.

Dr Danny Cheng
Chair and lead editor of SCP 4th edition v1.0 and v2.0
2018

6.

ONCOLOGICAL EMERGENCIES

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6. Oncological Emergencies

Introduction

Neutropenic sepsis is the commonest oncological emergency, and it is the most common cause of morbidity and mortality amongst children receiving chemotherapy for malignant conditions. Neutropenic sepsis is covered comprehensively in Chapter 3.

Most episodes of uncomplicated febrile neutropenia are managed effectively at a POSCU; on the other hand, the majority of other oncological emergencies require urgent transfer to a PTC for further management. However, it is important for POSCU's to understand this chapter because these emergencies are often recognised & diagnosed at the POSCU. After commencing initial management, it is vital for the POSCU to liaise with the PTC early to facilitate urgent transfer of these patients.

Ecthyma gangrenosum/Necrotising fasciitis

Cutaneous infection usually characterised by discoloured lesions or areas of skin (eg dusky, purple or black) in an immunocompromised patient. The commonest site is perineal skin, although this infection can occur in other parts of skin. Highly suspicious of Gram-negative infection, particularly Pseudomonas aeruginosa. Send blood cultures, local swabs and stool culture.

Ecthyma gangrenosum requires urgent treatment with intravenous antibiotics covering Pseudomonas and Gram-negative organisms. (iv piptazobactam and aminoglycosides as per neutropenic sepsis protocol is appropriate) Patients should be discussed with PTC for urgent transfer to PTC, surgical review and consideration of debridement.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) is a very serious and potentially life-threatening complication of children with a malignancy. Rapid cancer cell death (cytolysis) releases large amounts of uric acid, phosphate and potassium into the circulation. A secondary hypocalcaemia may result from hyperphosphataemia. End result being urate nephropathy and acute renal failure.

Whilst the onset of TLS is a true emergency, it can usually be prevented or treated, providing it is correctly anticipated. Prevention is the aim of management, using hyperdiuresis (via hyperhydration) together with allopurinol or rasburicase. TLS usually starts after induction of appropriate treatment; uncommonly TLS can also occur prior to chemotherapy. Duration depends on severity and supportive measures in place, but on average lasts for approximately 48 to 72 hours from start of treatment.

Figure 6.1 Tumour lysis syndrome flow chart 1: Prior to starting treatment/chemotherapy

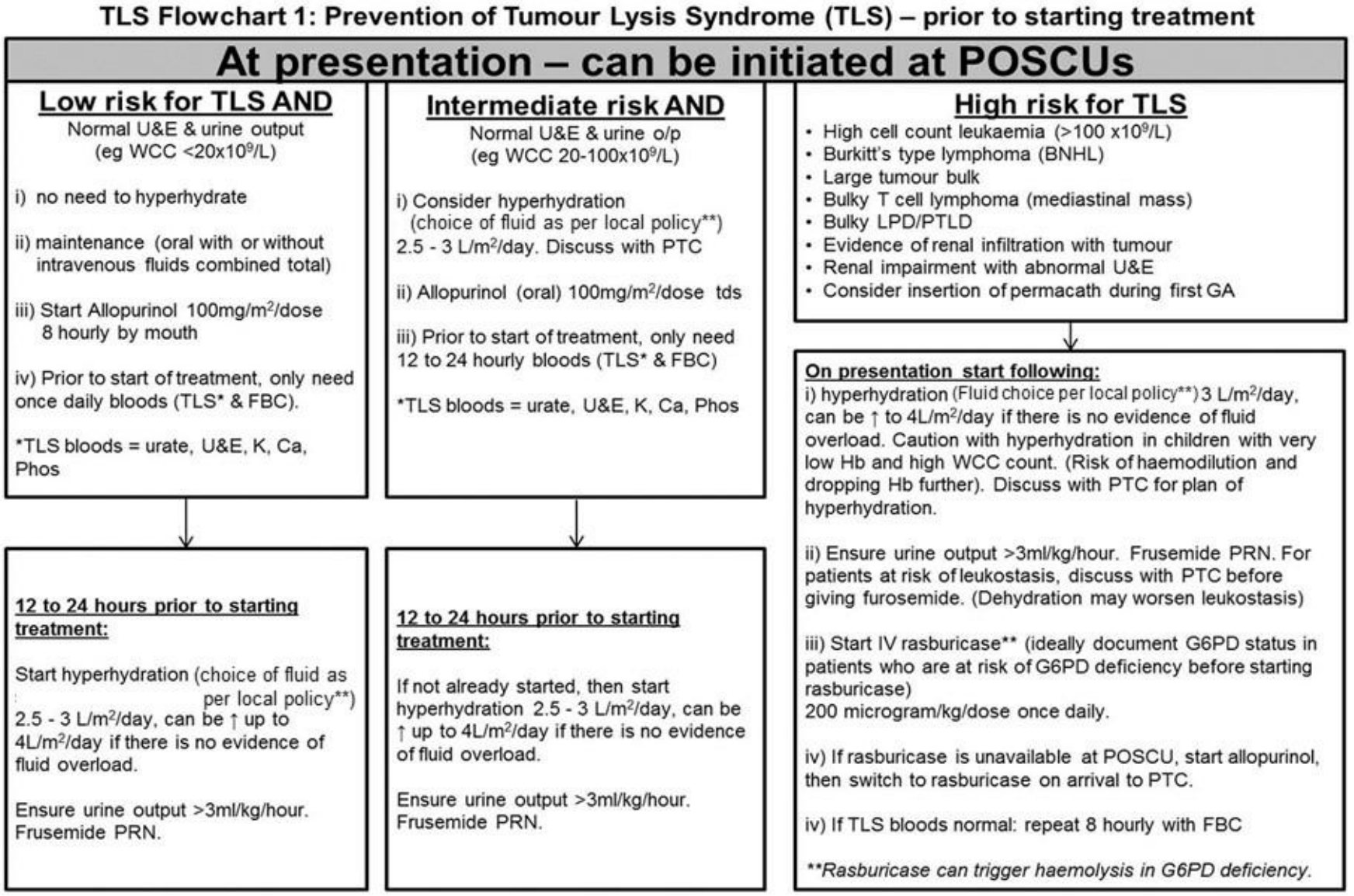
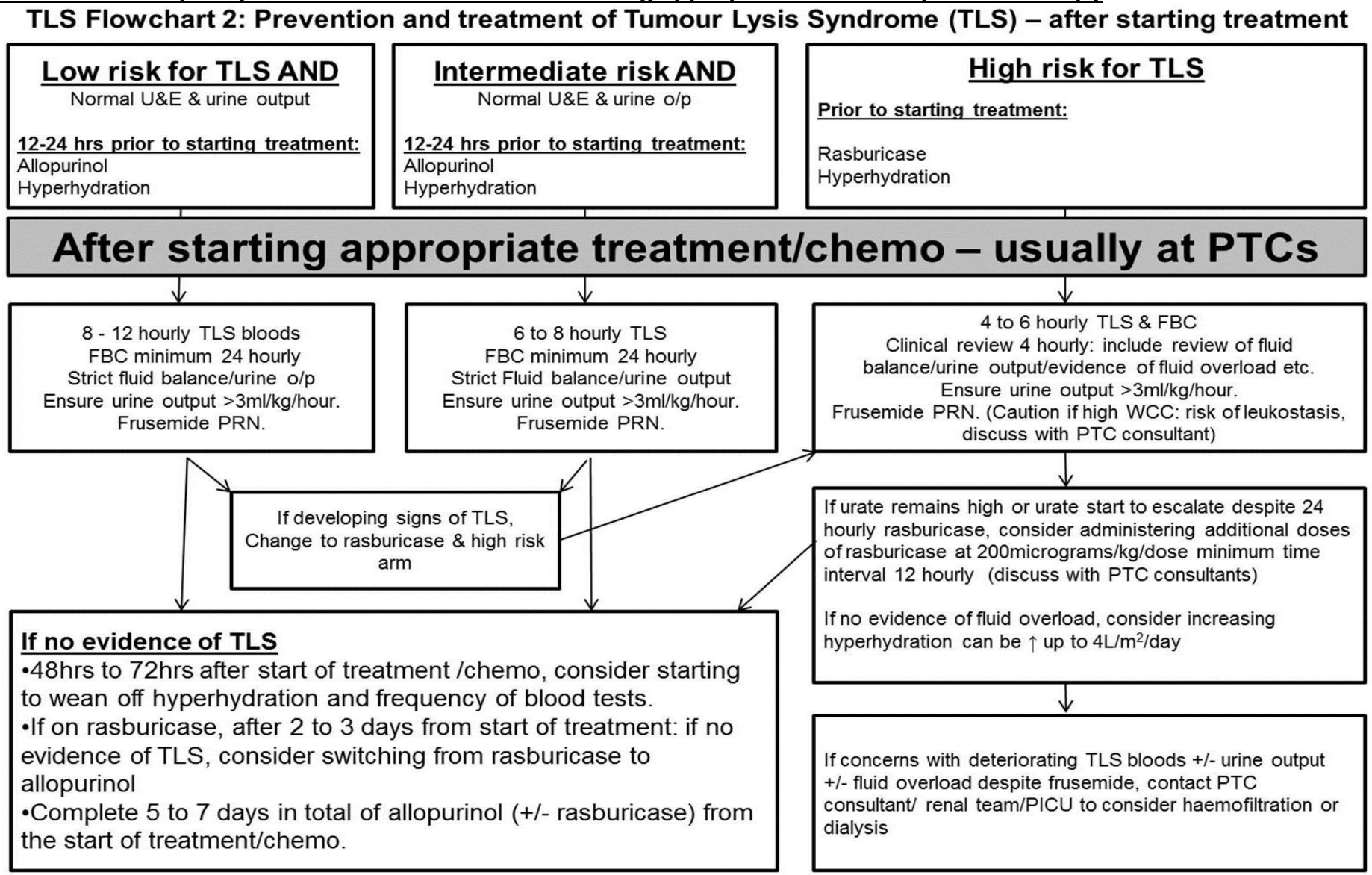


Figure 6.2 Tumour lysis syndrome flow chart 2: After starting appropriate treatment/chemotherapy



TLS may occur:

a) spontaneously (e.g. post-surgery)
b) as part of "unintentional" treatment (e.g. steroids given to a child with wheeziness caused by anterior mediastinal tumour, which has been misdiagnosed as 'new asthma'; or steroids given during general anaesthesia) or
c) following intentional therapy for a malignant tumour

Recognition of risk

RISKS	Examples	Typical prophylaxis
High risk of TLS		
Bulky, highly chemo sensitive malignancies	• Leukaemia with total white cell count usually in excess of 100 x10^9/L • Non-Hodgkin's lymphoma - B or T cell (e.g. large anterior superior mediastinal mass) • Large tumour bulk (e.g. large organomegaly) • Bulky lymphoproliferative disease (LPD) or post-transplant lymphoproliferative disease (PTLD) • Evidence of renal infiltration with tumour (e.g. on ultrasound) +/- Evidence of renal impairment (urea & creatinine)	Urate oxidase (Rasburicase)
Intermediate risk of TLS		
Widespread, chemo sensitive malignancies	* Leukaemia with total white cell count usually between 20 to 100 x 10^9/L – in the absence of large tumour bulk or renal impairment	Allopurinol
Low risk of TLS		
Widespread, chemo sensitive malignancies	* Leukaemia with total white cell count usually less than 20 x 10^9/L – in the absence of large tumour bulk or renal impairment * Non-bulky NHL, LPD or PTLD with normal renal function	Allopurinol
Unusual to develop TLS		
Most other tumours	* Solid malignancies * HLH	None

Diagnosis

Defining the criteria for the diagnosis of TLS is considerably less important than following the practical management plan outlined here. All the biochemical components may not be present initially and many of these measures can be instituted early to prevent progression to full blown TLS.

In patients who develop TLS, the biochemical abnormalities usually start to become evident 4 to 6 hours after initiation of appropriate treatment for the malignancy. The risk of TLS developing usually lasts until approximately 48 hours after starting appropriate treatment; after this time, the chance of TLS developing becomes much lower.

Initial management = Prevention (Fig. 1 and Fig. 2)

1. **Forced Diuresis/Hyperdiuresis/Hyperhydration**

    a. *Acute leukaemia with **WCC less than 20x10^9/L**, low disease bulk and in the absence of renal impairment*: in terms of hyperhydration, there is no need to hyperhydrate too early, as the risk of iatrogenic complications outweighs the benefit of preventing TLS in these patients. Allopurinol can be started, and it is usually sufficient for this sub-group of patients to receive maintenance fluid (orally and/or intravenously) before starting chemotherapy. Hyperhydration should be started 12 to 24 hours prior to start of steroids or chemotherapy.

    b. ***WCC between 20-100 x10^9/L,*** early initiation of hyperhydration can be considered and this should be discussed with PTC at the time of referral.

    c. ***High risk for TLS***: hyperhydration should be started early (e.g. start at POSCU)

    d. ***Caution with hyperhydration in patients with high count leukaemia and low haemoglobin*** - hyperhydration can cause further haemodiluation (i.e. lowering haemoglobin count). Remember packed red cell transfusion is a relative contraindication in high count leukaemia & leukostasis. Discuss with PTC.

    Choice of fluids depends on local policy; the most important being **DO NOT routinely add KCl (potassium chloride). Options include NaCl 0.9%/Glu 2.5%, NaCl 0.45% /Glu 2.5% etc.

    - In some subtypes of Acute Myeloid Leukaemia(M4/M5, myelomoncytic/monocytic), hypokalaemia (especially after initiation of leukaemia treatment) had been reported. This is thought to be due to raised renin activity and/or lysozyme levels. (Wulf et al 1996, Ann Hematol Sep;73(3):139-41. doi: 10.1007/s002770050215. Pickering & Catovsky 1973, *An International Journal of Medicine*, Volume 42, Issue 4, October 1973, Pages 677–682, https://doi.org/10.1093/oxfordjournals.qjmed.a067360).
    - In such circumstances, discuss with PTC consultant, as potassium supplementation may be required.

    If there is no evidence of fluid overload, greater rates up to maximum of 4 litres/m^2/day may be required for increasing metabolic disturbance.

2. **Allopurinol** 100mg/m^2/dose orally 3 times per day. Ideally this should be started at least 12 hours before commencement of chemotherapy and can be started before patient is transferred to PTC. Continue until 5 to 7 days after starting treatment. (note: dose different from BNFc. This is the same dose we have historically used for more than 20 years)

    Or Urate oxidase (Rasburicase) 0.2mg/kg/dose IV over 30 mins once every 24 hours. In established TLS, the frequency can be increased to 18 hourly to a maximum of 12 hourly (at same dosage). Rasburicase usage should be reviewed on daily basis. If rasburicase is unavailable at POSCU, start allopurinol, then switch to rasburicase on arrival to PTC. (note: no dose in BNFc. No change. Same doses as per previous SCP's)

    Note: ideally document G6PD status in patients who are at risk of G6PD prior to starting rasburicase. (Risk of rasburicase triggering haemolysis in G6PD deficient patients.) In exceptional cases, discuss with PTC consultant.

3. **Monitor urine output and strict fluid balance. Twice daily weights.**
    Ensure urine output of at least 3ml/kg/hour. Give furosemide if poor urine output and/or fluid overload. Note: furosemide is contraindicated in patients at risk of leukostasis.

4. **Monitor trend of electrolytes regularly - "TLS bloods"**
    a. Urate
    b. Potassium
    c. Urea & Creatinine
    d. Calcium & Phosphate

Suggested guideline for frequency of TLS bloods:

TLS risk group	Before starting treatment	After starting treatment
High risk	8 hourly	4 to 6 hourly
Intermediate risk	12 to 24 hourly	6 to 8 hourly
Low risk	24 hourly	8 to 12 hourly

Established tumour lysis

- Discuss and urgent transfer to PTC for further management
  as patient may require haemofiltration or haemodialysis via a permacath or vascath.

- **Apply cardiac monitor** (looking for evidence of peaked T waves and widened QRS complex of hyperkalaemia, and prolonged QT interval of hypocalcaemia).

- **Clinical review -** 4-hourly (looking for signs of hypocalcaemia such as vomiting, cramps, seizures, spasms, altered mental state and tetany; and of hyperkalaemia such as weakness and paralysis).

In particular circumstances, after discussion with PTC, it may be appropriate to:

- Catheterise patient if anuric or oliguric (ensures bladder is empty and accuracy of future measurements)

  Replace allopurinol with rasburicase (0.2mg/kg IV over 30 mins x 1/day). However, this should be avoided if patient known to have G6PD deficiency. Discuss with PTC (note: no dose in BNFc. No change. Same doses as per previous SCP's)

Emergency management of hyperkalaemia

(see also Chapter 13: fluid & electrolytes)

- Urgent repeat of biochemistry (blood gas machine for immediate result and urgent formal laboratory sample) Ensure free flowing venous sample. Special caution in high count, avoid excessive shaking of sample or pneumatic chute delivery system leading to artificially haemolysed samples.
- Discuss with PTC/renal physicians/intensive care retrieval team urgently. The measures outlined below should only be used under the guidance of PTC and renal physicians, as these measures will only transiently reduce the potassium level. Patients in established TLS with true hyperkalaemia require urgent haemofiltration or haemodialysis.
    - If ECG changes: Calcium gluconate
    - Give insulin & dextrose AND salbutamol TOGETHER (40-50% of patients are non-responders to salbutamol alone so avoid monotherapy). Repeat Salbutamol dose until ECG & K normalised.
    - BNFc for doses.

Leukostasis and Hyperleukocytosis

Patients with high count leukaemia (hyperleukocytosis) are at risk of death or serious complications due to leukostasis/hyperviscosity syndrome, coagulopathy, or tumour lysis syndrome. High count leukaemia is considered a haemato-oncological emergency. Hyperleukocytosis occurs in approximately 10-20% of acute leukaemia and the greater the white cell count, the greater the risk.

Recognition of risk/definition of "high count" in leukostasis:
Generally high-count leukaemia is defined as a white cell count of >100 x 10^9/l.

In monocytic AML (FAB type M5), high count is defined as >50 x 10^9/L as the malignant cells are large, tend to aggregate, and cause coagulopathy more readily.

Pathological definition: "Morphological evidence of intravascular accumulation of leukaemic blasts occupying most or all of the vascular lumen, with or without the presence of fibrin". It is thought that "sludging" of leukaemic blasts in capillary vessels lead to diffuse cerebral, pulmonary and renal microcirculatory failure, therefore tissue hypoxia, infarct or haemorrhage can occur as a result.

Diagnosis:
There are no diagnostic tests or criteria for leukostasis. Clinicians must have a high index of suspicion in patients who are at risk as defined above. Respiratory and CNS status must be reviewed regularly. Discuss with PTC consultants early if leukostasis is suspected.

Early signs include (CNS):	**Early signs include (Respiratory):**
• Headaches	• Dyspnoea
• Retinal haemorrhages	• Tachypnoea
• Papilloedema	• Oxygen desaturation
Progressing to:	
• Fluctuating / depressed CNS mental status	• Pulmonary infiltrates – diffuse, bilateral
• Focal CNS abnormalities	
• Seizures	
And ultimately:	
• Intracranial haemorrhages	• Respiratory failure

Coagulopathy, thrombosis & haemorrhagic stroke
Pro-coagulant molecules plus interaction with vascular endothelium may result in a consumptive ***coagulopathy***, or frank ***thrombosis***. Thus patients are at risk of haemorrhagic stroke.

Management

1) ***Prompt & URGENT transfer from POSCU to PTC***

2) ***If very high count (suspected) AML***: (e.g. above WCC 50x10^9/L, especially AML M4/5 and APML) liaise with PTC consultant urgently. *PTC consultant to consider urgent transfer to PICU (directly from POSCU) for exchange transfusion or leukapheresis (not recommended for APML). If PTC consultant deems the patient is at high risk of leukostasis and requires an exchange transfusion or leukapheresis, then the POSCU consultant will need to arrange immediate intensive care (CATS/STRS) transfer. ***The patient should arrive at PICU within 2 hours of referral to PTC.***

   If a PTC is unable to accommodate or accept a patient in this situation, there should be a PTC consultant to PTC consultant referral to ensure prompt transfer of the patient from the POSCU to an appropriate PTC.

Exchange transfusion/Leukapheresis is usually performed on PICU. This is usually not recommended for APML (AML M3) as this may worsen DIC.

3) ***CAUTION: AVOID Red Cell transfusion***

Packed Red Cells are very viscous with a high haematocrit (~70%) and transfusion may lead to clinical exacerbation of leukostasis; especially it may precipitate cerebral infarction and respiratory distress. Generally transfusion is avoided or very limited until the white cell count has been reduced to safe levels. ***Only administer Packed Red Cells after discussion with PTC consultant***. If PTC consultant agrees to red cell transfusion, patients should not receive more than 5ml/kg in a single transfusion, given over 4 hours. ***It is rarely needed to raise Hb to above 6g/dL by Pack Red Cell transfusion.*** If further blood transfusion is required, discuss with PTC consultant first.
[Volume (ml) of Packed Red cells = Desired rise in Hb (g/dL) x 3 x weight (kg). In high count leukaemia, maximum volume in a single transfusion = 5ml/kg]

4) ***Tumour lysis syndrome***: management, rasburicase (if indicated check G6PD before starting), hyperhydration and biochemistry monitoring as per GOSH Tumour Lysis Protocol.

5) Monitor FBC, coagulation and TLS bloods 4 to 6 hourly

6) ***Platelets*** - Maintain platelet count above 50 $x10^9$/L in the presence of active bleeding or coagulopathy, otherwise maintain platelets above 30 $x10^9$/L.

7) ***Coagulopathy*** – Coagulopathy is more common in AML than ALL but may occur in any leukaemia. In the presence of prolonged PT or APTT (>3 seconds above normal range) 10-15mls/kg of FFP should be given. Fibrinogen (aim for >1g/L) should be maintained with cryoprecipitate (5mls/kg). Further clotting tests should be sent following administration of FFP or cryoprecipitate. Should the clotting screen still be deranged, please discuss with consultant haematologist. In the event of active bleeding and coagulopathy, FFP and cryoprecipitate should be given according to the clotting parameters. Discuss with a consultant haematologist in this situation.

8) ***Children may deteriorate after starting cytotoxic therapy*** – a patient's respiratory and neurological status sometimes will initially worsen after starting cytotoxic chemotherapy, due to pro-coagulants released from dying cells. Close observation is mandatory.

9) ***Pulmonary infiltration and respiratory distress*** – Clinical signs of pulmonary infiltration/leukostasis include tachypnoea, dyspnoea and hypoxia. Clinically and radiologically, it is often difficult to differentiate pulmonary infiltration/leukostasis from fluid overload from hyperhydration. Fluid balance assessment, twice daily weight and careful clinical examination are important.

Furosemide should NOT be given as a routine - Avoid dehydration/volume depletion, as this may exacerbate leukostasis. Liaise with PTC consultant if patient is fluid overloaded.

10) ***Neurology*** - careful monitoring of neurological status. Clinical signs of CNS leukostasis include stupor, delirium, dizziness, altered mental status, tinnitus, ataxia, visual blurring, visual disturbance, papilloedema, retinal vein distension, retinal abnormalities. Clinical signs of abnormal neurology and raised intracranial pressure (headache, vomiting, neck stiffness, focal neurology, abnormal pupil reactions, deranged GCS etc.) may indicate cerebral infarction and/or intracranial haemorrhage. Careful and regular clinical assessment is mandatory. Inform consultant if patient develops neurological abnormalities.

11) ***Ophthalmology*** – very high-risk patients with coagulopathy are at risk of retinal haemorrhage. Ophthalmology review should be considered when patient has stabilized.

The definitive treatment and prevention of leukostasis is to commence chemotherapy urgently. Leukapheresis/exchange transfusion will only transiently reduce white cell count. Starting chemotherapy is a PTC consultant decision.

* Decision on whether patients need PICU & leukapheresis/exchange transfusion is multifactorial & beyond the scope of this protocol. This paragraph triggers the need of a PTC consultant experienced in managing these very high-risk patients to consider the risks, pros & cons of PICU leukapheresis & exchange transfusion.

Anterior mediastinal masses & Superior Vena Cava (SVC) obstruction

Children with an anterior mediastinal mass are a haemato-oncological emergency. This group of patients may experience serious and potentially fatal complications at presentation or during sedation/general anaesthesia, usually as a consequence of extrinsic compression of the airway, obstruction to the venous return or obstruction to the output of the heart. With modern chemotherapy regimens, the majority of children with an anterior mediastinal mass have an excellent long-term prognosis. Instigation of appropriate initial management can lead to avoidance of unnecessary morbidity and mortality.

Recognition

The undiagnosed child with a large anterior mediastinal mass may present in many ways and the classical features of SVC obstruction, signified by swelling of the upper thorax, head and neck with overlying superficial prominent & distended collateral veins, being infrequently observed. More often the anterior or middle mediastinal mass presents with respiratory &/or neurological symptoms or signs (see below). Posterior mediastinal masses rarely cause SVC or respiratory compromise.

Symptoms that should raise concern in any child with a mediastinal mass include:

Respiratory	Neurological
Chest pain	Headaches
Cough	Dizziness
Dyspnoea	Syncope
Orthopnoea	Episodic confusion &/or anxiety
Stridor	

Careful clinical assessment should be made since airway obstruction has been reported in up to 60% of patients presenting with mediastinal masses. Furthermore, a third of asymptomatic patients have a significant reduction in tracheal dimensions when assessed by CT.

Signs to be alert to:

Respiratory	Neurological	Cardiovascular
Tachypnoea	Papilloedema	Facial oedema
Cyanosis		Facial plethora
Wheeze		Distended veins
Reduced breath sounds		Pulsus paradoxus
Hypoxia		Hypertension

Not infrequently pleural and pericardial effusions may be associated with the mediastinal mass (typically T cell lymphoma / leukaemia). Pleural effusions may be bilateral and further compromise the child's respiratory status.

Diagnosis

BEWARE – inappropriately requested investigations may result in worsening respiratory compromise, rapid clinical deterioration and cardio-respiratory arrest!

CXR — include PA/AP and lateral to establish size of mass and whether the mass is anterior or posterior.

Chest CT — Only perform if it is safe for the patient. This test is not mandatory.
If significant mass on CXR and/or significant respiratory symptoms: **Avoid sedation or general anaesthesia, this may precipitate respiratory failure leading to death**
If respiratory symptoms deteriorate on lying supine, unsedated chest CT in supine position should be avoided. This may also precipitate acute respiratory failure. If patient can

tolerate lying prone or lateral without worsening of symptoms, CT chest may be considered in these positions. Discuss with PTC consultant.

Chest USS — If unable to perform chest CT, consider discussing with radiologist for chest/mediastinal ultrasound scan to assess mediastinal mass.

Blood tests — Baseline blood investigations (**FBC, blood film**, U&E, Phosphate, Urate, LDH, AFP & HCG) and urinary catecholamines should be performed as indicated and in discussion with PTC.

No further invasive investigations until the patient has been assessed by PTC consultant.

Management

- **Urgent transfer to PTC** – if significant mass on imaging and/or significant respiratory symptoms. Consider intensive care retrieval to PICU.

- **Close monitoring of the child is mandatory** including respiratory rate and saturations. Any child with hypoxia, orthopnoea, dyspnoea, stridor or marked tachypnoea requires anaesthetic review, urgent transfer to a PTC and potential PICU support, as in these situations emergency (empirical) chemotherapy or radiotherapy may be required.

- **AVOID** sedation and/or GA for any further investigations and contact PTC regarding transfer of the patient. Chest CT at this stage is contra-indicated in children with any respiratory or cardiac symptoms. These children should be referred to a tertiary centre on clinical suspicion; a CT is NOT required.

- **DO NOT** give steroids at this stage as there is a risk of initiating significant tumour lysis.

- If T-NHL / T-ALL suspected, then follow tumour lysis syndrome section.

- **If evidence of SVC obstruction** – avoid hyperhydration via upper limb, as there is a risk of exacerbation of facial swelling and cerebral oedema in SVC obstruction. Hyperhydrate via lower limb cannulae only

- On arrival to PTC, review by PTC consultant to decide whether empirical treatment should be initiated immediately without tissue diagnosis.

Other causes of SVC obstruction

Superior vena cava obstruction is associated with:

- **Obstruction of the SVC** secondary to an **anterior** mediastinal mass (lymphomas – typically NHL, leukaemia – typically T-ALL, thymoma and teratoma), complicates approximately 10% of mediastinal mass presentations.
- **Thrombosis within the SVC** (usually related to central venous catheters).

The child with a known malignancy and on active treatment whom presents with SVC obstruction is likely to have a central venous catheter related thrombus. In these situations the central line is likely to have stopped functioning adequately, which may be the initial presenting symptom. Alternatively, the child may present with classical features of SVC obstruction (swelling of the upper thorax, head and neck with overlying superficial prominent & distended collateral veins). Investigations that would be recommended and may have been performed in coming to the diagnosis are a CXR and Echocardiogram. Screening for prothrombotic tendencies may be requested although baseline bloods and a clotting screen will usually suffice until the child is seen at the PTC.

In these situations the child will require transfer to the PTC for removal of the catheter +/- thrombus excision, followed by anticoagulation.

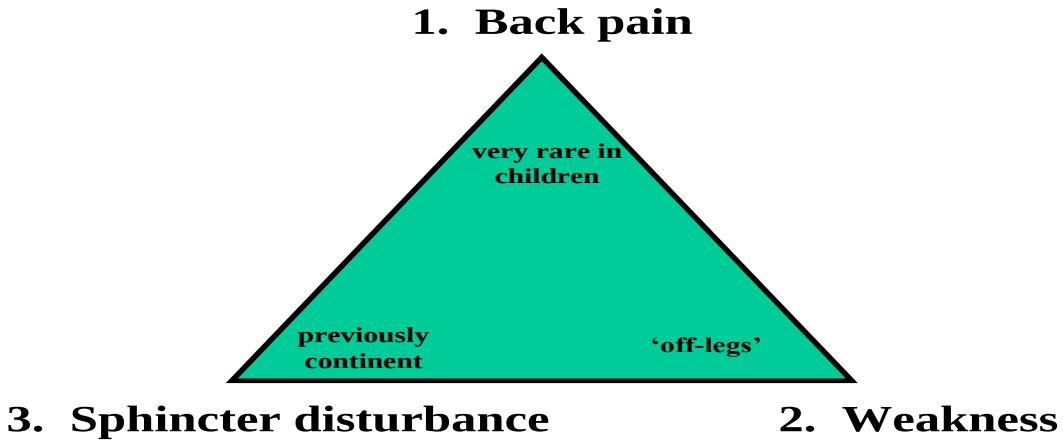
Spinal cord compression (SCC)

Spinal cord compression is relatively uncommon but requires urgent attention to avoid irreversible sequelae. It complicates 4-7% of all childhood malignancies from presentation to completion of treatment. In the majority of SCC cases, presentation is in the terminal phases of relapsed or progressive malignancy, but 25% of cases are in undiagnosed children during their first presentation. Other causes of spinal cord compression include infection (osteomyelitis, paraspinal/spinal abscesses), vertebral collapse and haematomas/infarction, which may occur in oncology patients during their treatment phase.

Approximately half of all SCC cases are caused by neuroblastoma or Ewing's tumours. Thereafter, rhabdomyosarcoma, other soft tissue sarcomas and osteosarcoma account for the majority of the remaining incidences, although almost any metastatic tumour can result in SCC. Compression typically results from direct tumour extension through the intervertebral foramina to impinge upon the spinal cord (the so called 'dumb-bell' tumour), although primary/intramedullary CNS tumours of the spinal canal may present in a similar fashion.

Recognition

Classical symptom triad:



In older children/adolescents, back pain is typically the first symptom and will precede neurological dysfunction by hours to months. Weakness is usually symmetrical (presenting with an unsteady gait through to paraplegia or quadriplegia) and may be associated with sensory dysfunction, and the insidious onset of loss of sphincter control. Signs are appropriate for the level of the SCC with a sensory level, muscular weakness, increased tone, clonus and extensor plantar reflexes. Tenderness to palpation is often present. A palpable bladder is a sinister sign in this context!

Particular care must be taken in assessing possible spinal cord compression in young, pre-ambulatory children when the signs may be subtle. It is particularly important to distinguish loss of motor milestones (i.e. regression) from developmental delay since the former is considerably more concerning for spinal pathology. In older children, whilst weakness of the lower limbs may be due to Guillain-Barré Syndrome, spinal cord compression must also be considered, and MRI spine is advised.

Diagnosis

- **The investigation of choice is an MRI of the spine**. This may be requested from the POSCU in discussion with the PTC as it may result in less delay before definitive treatment (chemotherapy,

radiotherapy or neurosurgical decompression) is commenced. A CT may reveal paraspinal pathology; however a *normal spinal CT does not necessary exclude intraspinal pathology*. Liaise with PTC.

- Standard initial investigations as determined locally with FBC and film, Biochemistry and Clotting screen. Additional serum for AFP/HCG, LDH and urinary catecholamines may be required, although is likely to be performed at the PTC since there should be minimal delay in transferring the patient.

Management

- **Contact PTC** to arrange early transfer and further investigations.

- Start dexamethasone **URGENTLY**. The only proviso to this is that there should be no other features suggestive of lymphoma (anterior mediastinal mass on CXR/lateral or CT, hepatosplenomegaly & peripheral blood film with blasts present), although it should be remembered that this is **rare**. If in doubt discuss with PTC.

- ***Suggested dose of Dexamethasone intravenously or orally for raised ICP & spinal cord compression is 10mg/m2/day in divided doses.*** This can be divided into 2 to 3 doses, up to maximum capped dose of 4mg per dose 4 times daily or 8mg per dose 2 times daily (ie 16mg in 24 hours)

    - Note: there is no publish data on recommended doses of dexamethasone for raised ICP or spinal cord compression. This dose is based on discussions with and recommendations from neuro-oncologists and neurosurgeon at GOSH*. This dose can be adjusted according to response in liaison with PTC and neurosurgeons.

      * With thanks to Professor Darren Hargrave, consultant neuro-oncology, GOSH;
      Dr Antony Michalski, consultant neuro-oncology, GOSH;
      Mr Kristian Aquilina, consultant neurosurgeon, GOSH.

- Commence appropriate analgesia for the presenting pain and discomfort (refer to Chapter 12 – Basic principles of symptom management for further guidance).
- Useful reference for subsequent management: Guidelines for Management of Neurogenic Bowel Dysfunction in Individuals with Central Neurological Conditions - Initiated by the Multidisciplinary Association of Spinal Cord Injured Professionals (last read 10/3/23)

Raised intracranial pressure

Primary CNS tumours are not discussed in any great detail throughout the supportive care guidelines since the referral pathway is via the neurosurgeons. The management of raised intracranial pressure should be in discussion with the neurosurgeons and depends upon local policy, as this complication is neither specific nor peculiar to oncology patients.

However, cerebral herniation may result from an expanding mass within the fused skull vault, or from obstruction of the CSF channels. This may occur in primary CNS or metastatic extracranial tumours but also in cases of intracranial haemorrhage, thrombosis, infarction or abscess formation, which may also occur in the oncological patient.

Recognition

Be aware of this complication in children presenting with headache, nausea and vomiting (particularly effortless early morning vomiting that relieves the headache), a stiff neck and papilloedema. Impending cerebellar herniation may be suggested by impaired conscious level, focal neurological signs (particularly abnormal extraocular movements and unequal pupils with sluggish light reflexes), and hypertension with bradycardia (the Cushing Reflex).

Management

- Discuss with appropriate neurosurgical unit and involve local anaesthetic team. Urgent time-critical neurosurgical transfers will have to be performed by the local anaesthetic team, discuss urgently with neurosurgeons and CATS/STRS. Less urgent cases will be transferred by CATS/STRS.

- Head CT or MRI urgently

- AVOID strong opiate analgesia, since this makes monitoring of the child more difficult and will affect papillary reflexes prior to intubation. Once the child is anaesthetised and ventilated it is appropriate to use morphine to maintain sedation whilst transferring a child to PICU and will not mask papillary responses. It is essential to monitor papillary signs in these patients frequently (5-15 minute intervals).

- In discussion with PICU/anaesthetic support and neurosurgeons consider elective intubation and normocarbia, and/or dexamethasone, and/or osmotherapy.

- ***Suggested dose of Dexamethasone intravenously or orally for raised ICP & spinal cord compression is 10mg/m2/day in divided doses.*** This can be divided into 2 to 3 doses, up to maximum capped dose of 4mg per dose 4 times daily (ie 16mg in 24 hours)

    - Note: there is no publish data on recommended doses of dexamethasone for raised ICP or spinal cord compression. This dose is based on discussions with and recommendations from neuro-oncologists and neurosurgeon at GOSH*. This dose can be adjusted according to response in liaison with PTC and neurosurgeons.

      * With thanks to Professor Darren Hargrave, consultant neuro-oncology, GOSH;
      Dr Antony Michalski, consultant neuro-oncology, GOSH;
      Mr Kristian Aquilina, consultant neurosurgeon, GOSH.

- Osmotherapy, indication to be discussed with neurosurgeons or PICU - mannitol dose as per BNFc (electronic BNFc last seen on 9/10/18. If BNFc subsequently update these doses, the authors recommend to use updated doses in latest updated version of BNFc):
    - 1 month to 11 years: 0.25–1.5 g/kg, repeated, if necessary, to be administered over 30–60 minutes, dose may be repeated 1–2 times after 4–8 hours
    - 12 to 17 years: 0.25–2 g/kg, repeated, if necessary, to be administered over 30-60 minutes, dose may be repeated 1–2 times after 4–8 hours

Seizures and status epilepticus

As per local or APLS guidelines for any child presenting with seizures.
See also Chapter 12 – Basic principles of symptom management for further guidance.

Acute hypertension and hypertensive encephalopathy

This is dealt with in detail in Chapter 11 – Hypertension. Hypertension is not an uncommon problem and may be seen as part of the presenting features for certain tumours (particularly neuroblastoma, phaeochromocytoma and nephroblastoma), or as a consequence of treatment (especially steroids during induction chemotherapy for ALL). Maintaining a normal blood pressure with intermittent oral anti-hypertensives is essential to avoid complications associated with prolonged hypertension and precipitation of an acute hypertensive crisis or encephalopathic illness (hypertensive or posterior reversible leukoencephalopathy syndrome).

The acute hypertensive crisis is best dealt with using IV anti-hypertensives and requires anaesthetic/PICU support in many cases. Discuss urgently with the PTC.

Intestinal obstruction and typhlitis

Gastro-intestinal tract (GIT) obstruction, pseudo-obstruction and ileus are infrequent problems and rarely precipitate acute emergency situations. Mucositis and constipation are much more common problems and have been discussed at length in Chapter 10 Mucositis and Chapter 12 – Basic principles of symptom management: constipation section.

On occasions a child presenting with acute intussusception is diagnosed with abdominal lymphoma (usually Burkitt's type) or rarely another malignancy. The management of intussusception typically precedes the diagnosis of malignancy (although suspicions are raised in older children with irreducible or recurrent problems) and the medical management is unchanged by the underlying cause.

Acute or sub-acute/pseudo bowel obstruction may follow chemotherapy or be as a consequence of abdominal surgery after tumour resection and usually settles with conservative treatment i.e. nil by mouth, large bore NG tube on free drainage, IV hydration +/- IV antibiotics. It may be necessary to alter

drug doses with future chemotherapy courses (notably vincristine), so please inform the PTC. If the patient has undergone recent abdominal surgery, transfer back to the paediatric surgeons may be required.

Typhlitis

This is neutropenic enterocolitis. It most commonly occurs in the caecum and typically follows a prolonged course of neutropenia, resulting in benign mucosal ulceration, bacterial invasion and bowel perforation & peritonitis.

Recognition/Diagnosis

The symptoms suggest inflamed bowel with any/all of abdominal pain, nausea & vomiting, bloody/watery diarrhoea being present. There may be absent bowel sounds, high fevers and the child may be clinically shocked due to sepsis.

♦ BEWARE – the symptoms are masked by steroids and the presence of a rigid board like abdomen typical of peritonitis will not necessarily be present. Hence the child in the latter half of induction chemotherapy for ALL may present atypically. Investigations should include those for febrile neutropenia, along with AXR and erect CXR looking for pneumatosis coli or evidence of perforation and an ultrasound of the abdomen.

Management

- Treatment is initially conservative (as per bowel obstruction above)
- Broad spectrum antibiotics are required immediately to cover the sepsis (as per febrile neutropenia policy but add in metronidazole as well for anaerobic cover).
- If the child is significantly unwell (hypotensive not responding to fluid bolus, then transfer to the PTC or PICU may be warranted for inotropic support – please discuss).
- If the symptoms do not settle rapidly, surgical intervention may be required, so liaison with the PTC and paediatric surgeons is necessary, not least as the mortality due to typhlitis is high!

Pancreatitis

This is an uncommon but important cause of abdominal pain in haematology-oncology patients, usually (but not exclusively) caused by the use of asparaginase. Other drugs such as steroids may also be risk factors.

Recognition
Classically the pain is epigastric, of sudden onset, gradually intensifying, then becoming constant and radiating through to the back. Clearly, however, it is rare to obtain such a history in children and the index of suspicion should be high in any child post-asparaginase presenting with abdominal pain. There may be associated nausea or vomiting, fever, tachycardia and, in severe cases, tachypnoea. There is usually upper abdominal tenderness, with or without guarding, abdominal distension and reduced bowel sounds. The Grey Turner and Cullen signs are very rare in children.

Diagnosis
Initial investigations should include a blood gas, glucose, amylase and lipase. The lipase is much more specific than the amylase, and levels more than 3x the upper limit of normal are usually due to pancreatitis. It should be borne in mind, though, that both the amylase and the lipase can fall in the later stages of worsening pancreatitis and can even be within the normal range. Further investigations should therefore be carried out if there is a clinical suspicion of pancreatitis even if the enzyme levels are normal.

The definition of pancreatitis used in UKALL 2011 trial is provided here as reference (UK clinical guidelines; - Gut 2005, 54)
For the purpose of UKALL2011 trial, pancreatitis is defined on the basis of at least two of the following features,

1. Abdominal pain strongly suggestive of acute pancreatitis

2. Serum amylase and/or lipase ≥3 times the upper limit of normal (lipase is preferred over amylase due to greater specificity)

3. Characteristic imaging findings of acute pancreatitis (ultrasonography is often unhelpful but contrast enhanced CT or MRI/MRCP may be useful for both confirming the diagnosis, determining severity, assessing complications, and for guiding potential percutaneous interventions).

Management

- *Patients should be managed in the PTC, with close input from the gastroenterologists and pain team*.
- Initial treatment comprises fluid resuscitation as appropriate, bowel rest and appropriate analgesia.
- A nasogastric tube (NGT) should be sited for symptom relief and IV fluids commenced
- Close attention to fluid balance.
- It is often necessary to administer PN whilst waiting for the symptoms to settle.
- Ketamine is preferred to morphine for pain relief.
- In severe cases octreotide can be helpful. Discuss with gastroenterologists

- Strictly speaking, antibiotics are not beneficial for pancreatitis. However, it is usually appropriate for them to be prescribed, as children with pancreatitis are often very unwell and neutropenic, therefore sepsis cannot be excluded.
- As symptoms settle, feeds can be slowly reintroduced. In mild cases it may be possible to reinstitute feeds via the NGT in the form of easily digestible medium chain triglycerides (MCT). In more severe cases, feeds should be given via a nasojejunal tube (NJT).
- Complications, such as severe haemorrhage, intestinal obstruction/necrosis and pseudocyst formation are very rare but should be looked out for.
- Repeat imaging and referral to the paediatric surgeons may occasionally be required.

Coagulopathy/DIC

There are many reasons for acute haemorrhage in oncology patients before or during treatment, some of which are shown below:

Problem	Possible causes	Products to be considered
Thrombocytopenia	Lack of production (e.g. bone marrow infiltration or suppression, Fanconi's anaemia or thrombocytopenia absent radius TAR syndrome)	Platelet pool (10-15mls/kg over 20-30 mins)
	Increased destruction (e.g. sepsis syndrome, ITP or TTP)	
	Sequestration (e.g. hypersplenism)	
	Hereditary (e.g. Wiskott-Aldrich or Bernard-Soulier syndrome)	
Coagulopathy	Increased consumption of clotting factors such as DIC (e.g. sepsis syndrome or AML-M3) & Fibrinogen depletion (asparaginase therapy)	Cryoprecipitate (5-10ml/kg over 20-30 mins) &/or FFP (10-15ml/kg over 20-30 mins)
	Decreased production of clotting factors (e.g. liver dysfunction or infiltration)	Vitamin K 0.3mg/kg IV slowly (max. 10mg) +/- FFP (10-15ml/kg over 20-30 mins)
Acquired anticoagulants	Inhibitors against coagulation factors (e.g. antiphospholipid antibodies)	Prolonged APTT, but propensity to acute thrombosis (call PTC)
Acquired von Willebrand`s disease (vWD)	Wilms' tumour associated	As per hereditary vWD (call PTC)
Direct effects	Erosion of blood vessels (e.g. by tumour or fungus) & venepuncture (insertion of central venous catheter)	Local haemostasis

Investigation
Check FBC, clotting screen, D-dimers (for DIC), acquired anticoagulants, clotting factors as appropriate.

Management
In most cases the bleeding can be controlled with appropriate blood product support and also, where appropriate, local haemostasis (e.g. ENT nasal packing for epistaxis). Please see chapter 2 on the 'Use of Blood Products', for details on appropriate transfusions, indications and dosing. Coagulation and FBC should be monitored regularly, 6-8 hourly, and acted on accordingly until transfer of the patient to the PTC. Ultimately, correction of the coagulation disorder requires treatment of the underlying cause, which may include:

- Chemotherapy
- Appropriate antimicrobials if sepsis syndrome
- Vitamin K for liver failure

As previously mentioned, coagulopathy is occasionally associated with hyperleukocytosis or tumour lysis syndrome. Additionally, it is a potentially life-threatening complication of AML-M3 (Acute Promyelocytic Leukaemia) at presentation or following induction chemotherapy and is the commonest cause of induction deaths in APL.

- All children thought to have Acute Leukaemia, should have a clotting screen performed promptly.
- Where APL is considered platelet counts should be kept above $30x10^9$/l
- Coagulopathy should be anticipated in high count leukaemia
- Please discuss with PTC, but in established coagulopathy, platelets, FFP and cryoprecipitate are likely to be required (see Chapter 2).

Cardiac dysfunction & tamponade

Congestive heart failure (CHF) is a rare initial presentation in some children with cancer due to profound anaemia or as a consequence of treatment (anthracycline-induced myocyte damage).

Recognition

The presentation is no different to any other child in heart failure with breathlessness (poor feeding in infants), weight loss/failure to thrive and sweating. There may be associated anaemia, tachypnoea, respiratory distress, elevated venous pressure and hepatomegaly.

Diagnosis

Typical investigations include:

- Baseline bloods
- CXR (enlarged cardiac shadow)
- ECG (various non-specific abnormalities seen in CHF +/- low voltages may be seen in anthracycline induced cardiomyopathy)
- Echocardiogram will determine cardiac function and is used to monitor response to treatment.

Management

- Discuss with PTC and paediatric cardiologists – urgency for transfer for assessment will depend upon underlying aetiology, clinical state and response to treatment.

- Initial treatment is with diuretics in CHF (however, if secondary to profound anaemia a top up transfusion and usual management for a new patient with malignancy is advocated, although diuresis may still be required).

- **Cardiogenic Shock** – this is a rare cause of shock in haemato-oncological patients. However, it is important to remember that the standard treatment for shock (with septic shock being the commonest in haem/onc patients) with fluid boluses and volume expansion will lead to clinical deterioration and worsening cardiac failure in patients with known heart failure. Clinicians must discuss with cardiologists the management of shock in a patient with known cardiac failure.

Cardiac tamponade

Cardiac tamponade is an exceptionally rare complication of malignancy despite the relative frequency of pericardial effusions at presentation.

Recognition:

Clinical features at presentation may relate to the underlying malignancy but also with evidence of CHF as documented above. Additional features may include chest pain, cough, hiccups, non-specific abdominal pain and pulsus paradoxus.

Diagnosis:

- CXR reveals the enlarged 'boot-shaped' cardiac shadow
- ECG low voltages with flattened or inverted T waves
- Echocardiography is diagnostic.

Management:

- Discuss with PTC and paediatric cardiologists since percutaneous drainage is the treatment of choice for symptomatic relief. Additionally, the effusion may be diagnostic if tumour cells are identified on cytology &/or cytospin with immunophenotyping. Definitive treatment is the appropriate treatment for the primary tumour!

- Diuretics may have a limited role to provide some symptom relief, thereby enabling transfer – discuss with PTC.

Veno-occlusive disease

Veno-occlusive disease (VOD) of the liver (or sinusoidal occlusion syndrome [SOS] as it is also known) is a serious regimen-related toxicity that typically follows bone marrow and stem cell transplantation. However, it can be seen following traditional chemotherapeutic schedules. Regimens including thiopurines, (typically thioguanine during the intensification blocks) may predispose to a typically more insidious but nonetheless significant form of VOD. Actinomycin D may also precipitate VOD.

Recognition/diagnosis

Classical clinical findings are a triad of weight gain, ascites and tender hepatomegaly. This may be associated with abnormal LFTs, thrombocytopenia, which tends to be refractory to platelet transfusions and reversal of portal blood flow on ultrasonography. (The latter is not required to make the diagnosis, since this is a very late feature of the syndrome). If clinical and/or ultrasound findings are consistent with this, then thioguanine, actinomycin D or presumed precipitant should be stopped, and re-exposure avoided.

Management

General recommendations for the supportive care of VOD are as follows:

- Discuss with PTC, patients with suspected VOD should be transferred to PTC for further management.
- Careful monitoring of fluid balance (including twice daily weights and abdominal girths) and avoidance of sodium loads.
- Fluid restriction.
- Diuretics as indicated (excessive positive balance or weight gain) aiming for equilibrium.
- Opiate analgesia as indicated (i.e. right upper quadrant pain).
- BEWARE - patients with severe VOD and multi-organ failure are at increased risk of infection. Therefore if clinical concerns or fever, commence antibiotics as per febrile neutropenia protocol.
- PN is likely to be required, and should this be instigated, lipids should be avoided due to the likelihood of increasing liver damage.
- Should ascites cause respiratory compromise, paracentesis may be appropriate, but should be performed with caution and careful attention to coagulation parameters.
- Careful observation in severe cases for ensuing renal and pulmonary failure requiring haemodialysis and mechanical ventilation – Liaise with PICU as required.
- Use of defibrotide (discuss with PTC consultant).

Extravasation

Should a known vesicant extravasate (anthracyclines or vinca alkaloids) prompt action **must** be taken. This is covered in detail in Chapter 8 – Extravasation.

Post-Asparaginase observations & monitoring for allergic reactions

Introduction

Asparaginase is a very effective and important drug used as part of multi-drug treatment plans for acute lymphoblastic leukaemia. Allergic reactions are the commonest serious adverse events; there is a highly variable frequency reported in literature (between 3-75%[1]). Incidence of reactions is dependent on asparaginase formulation and dosing etc.

The most common formulations used across London are PEG-asparaginase (Oncaspar) and Erwinia asparaginase. PEG-asparaginase has much longer half-life and is thought to have higher incidence of allergic reactions, especially late reactions. Erwinia asparaginase has short half-life and is less commonly associated with late reactions.

Rationale for change of practice and policy

Historically, many units' policy in the past was to monitor patients in hospital for 1-hour post asparaginase administration. Majority of the time, no further instructions were given to parents post this 1-hour observation period; specifically, there was no parental advice on school attendance or parental observations at home.

Highest risk period (0 – 2 hours): Henriksen et al (2015)[1] demonstrated 58% of patients developed allergic reactions within 2-hours after PEG-asparaginase; there was just-under-40% of patients with severe reactions of grades 3 or 4. (Fig 4)

Low to moderate risk period (2 – 6 hours): significant proportion of patients (approximately 30%) developed reactions between 2 to 6 hours; 10% or so had grade 3 reactions (no grade 4 reactions reported beyond 2 hours).

Low risk period (6 – 24 hours): as per Fig 4, there were still roughly 2 to 3 % of patients who had grade 3 reactions in the >6-to-<=12-hour and >12-to-<=24-hour periods.

Henriksen et al (2015)[1]

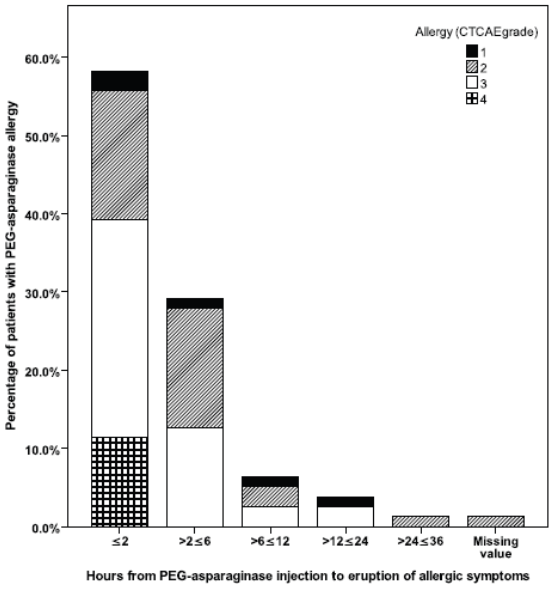


Fig. 4. Time (hours) from PEG-asparaginase administration to development of allergic symptoms. Patterns denote the severity of allergy CTCAE grade 1–4 (NCI Common Terminology Criteria for serious Adverse Events). Grade 1 being a mild allergic reaction and 4 being an anaphylactic reaction. Patients in total (N = 79).

Guidelines for post-asparaginase observations and monitoring

Based on data published by Henriksen et al (2015)[1], the previous policy of post-asparaginase monitoring was inadequate, and the following recommendations were made

1 Day cases: ideally aim to administer asparaginase before midday [a].

2 Observe by trained healthcare professionals on day-unit for minimum of 2-hours (ie during highest risk period). Monitor temperature, heart rate, respiratory rate, blood pressure, capillary refill time, signs & symptoms of mild/severe reactions (as per [b] below) at:
- 1-hour post-asparaginase
- 2 hours post-asparaginase

3 At 2-hours post-asparaginase administration, if all observation stable and without signs or symptoms [b] of allergic reactions, patients may be discharged for continued monitoring and observations by educated parents/carers/ responsible adults.

4 Before discharge, ensure parents/carers/responsible adults had been educated on:
- if available, provide Parent Information Leaflet (PIS) on Parental monitoring post-asparaginase after discharge.
- For each episode, parents should be given the written time ranges of risk periods

Low to moderate risk period (2 – 6 hours): Between 2 to 6 hours post-asparaginase, it is recommended patients should NOT be left unattended for prolonged periods; and ideally not to attend school. I.e. a responsible adult (with knowledge of what to monitor and actions to take) should be near patient, and patient is not left alone by him/herself in separate room. (e.g. prolonged unsupervised afternoon naps in child's own bedroom and away from parent/responsible carer etc)
- If mild reactions, contact Paediatric Oncology Shared Care Unit (POSCU) immediately.
- If severe reactions, dial 999, then contact POSCU.

Low risk period (6 – 24 hours): Between 6 to 24 hours after asparaginase, there is still very small chance (2-3%) of severe reactions. However, pragmatically, it cannot be expected for patients to be continuously observed for 24 hours at home. Parents only need to be informed of an ongoing, albeit very small risk of severe reactions between 6 to 24 hours post-asparaginase. And if possible, monitor more frequently than usual.

Rationale & notes:

[a] If given before midday, then majority of grade 3 or 4 reactions should occur before 6pm. For day cases, if administration must be given after midday, POSCU team should risk assess on individual basis. Especially focusing on whether patients will be unsupervised for prolonged periods (eg bedtime) during the low to moderate risk period.

For inpatients: time of administration is less strict, as patients will be observed by professionals as inpatients 24/7. Thus, it is acceptable to give asparaginase to inpatients in afternoon. But it is still recommended for inpatient nurses to do similar observations as per day cases above.

b **Mild reactions:** skin rashes, itching, redness and/or swelling around injection site, high temperature, shivering, redness of face, mild dizziness or headache.

Severe reactions: any signs or symptoms of mild reactions, as well as any of following:

- Severe swelling of tongue and/or throat
- Shortness of breath
- Difficulty talking or hoarse voice
- Appearing very pale or blue and clammy
- Decreased level of consciousness: severe dizziness, faintness, blackout, floppy, disorientation, unresponsive
- Collapse

Note: as routine for majority of clinical studies, Henriksen et al (2015)[1] reported reactions using CTCAE grading system[2]. For this SOP, the more clinically useful definitions of mild and severe reactions are used instead.

PEG-asparaginase: Above steps to be followed for every dose of PEG-asparaginase administration.

Erwinia asparaginase: steps 1) to 4) only need to be done for the first dose of each block of Erwinase.

After a block had started (ie from dose 2 to dose 6 or 7), patients should be observed by healthcare professionals for 2-hours. There is no need for strict parental observations post discharge. (For Erwinia asparaginase, the risk of late reactions is much lower. In the small cohort reported by Henriksen et al (2015)[1], all reactions occurred within 2-hours of administration. Although it is noteworthy the numbers are very small in this series).

Reference

1 L.T. Henriksen et al (2015) PEG-Asparaginase allergy in children with Acute Lymphoblastic Leukemia in the NOPHO ALL2008 Protocol. Pediatr Blood Cancer 2015;62:427–433

2 CTCAE (Common Terminology Criteria for Adverse Events) [Last read on 7th December 2022)

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. **Navigational Note:** If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					

7.

CARE OF CENTRAL VENOUS ACCESS DEVICES

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7. Central Venous Access Devices

General Information: Central Venous Access Devices (CVAD)

Vascular access plays an integral role in the delivery of intravenous therapy and blood sampling in haematology and oncology patients. Making the right choice of vascular access device for patients is critical, as is the subsequent care of both the patient and their device (Capital Nurse, 2020). This chapter will discuss the different types of devices haematology and oncology patients may have and how these are cared for. This chapter will cover generic information for each type of device, however, may not be brand specific. If a patient is discharged and the care required for their CVAD differs from information available in this chapter, the PTC will let you know.

For further information on Intravenous therapy and CVADs, Great Ormond Street Hospital and other PTCs in London are following the Capital Nurse IV therapy passport developed by Higher Education England (HEE). The IV passport has been endorsed by the Royal College of Nursing until June 2023 and is free of charge for health care professionals to access at the time this chapter is published (HEE, 2023).

What is a Central Venous Access Device?

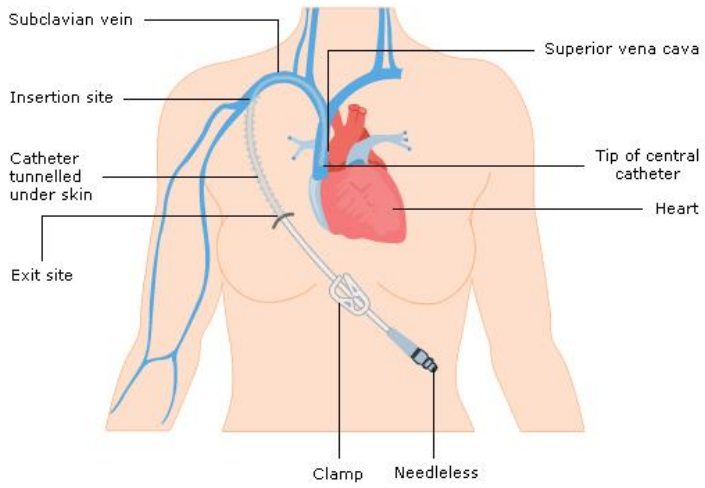
A central venous access device (CVAD) is a catheter inserted into the central venous system, the internal tip of which sits within the superior/inferior vena cava, or the right atrium.
CVAD's are generally inserted at a patient's Principal Treatment Centre (PTC), and there are many different brands of CVAD's that may be used. The brand and size of CVAD should be recorded in the patient's medical notes, and this information available on discharge from the PTC.

CVAD insertion, maintenance and care should adhere to local trust Central Venous Care Bundles. All those who use CVAD's must have knowledge of, be trained and be deemed competent in their local area to use and care for these devices.

Types of CVADs

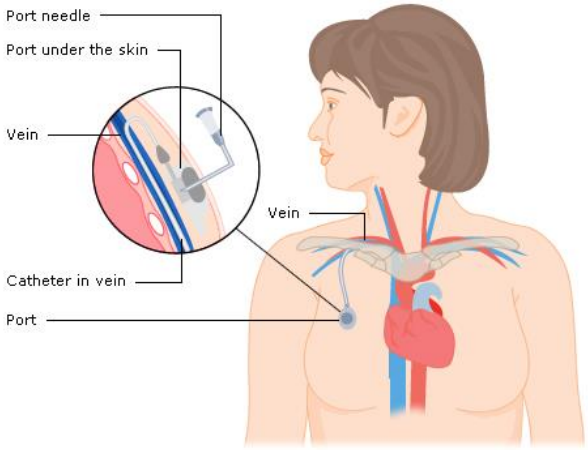
Skin Tunnelled Cuffed Central Venous Access Devices

A skin tunnelled CVAD is a tube that is tunnelled under the skin of the chest wall to a vein in the neck. From there it is threaded through a large vein into the Superior Vena Cava or the right atrium. The line may separate into one, two or three separate lumens depending on the patient's treatment needs.

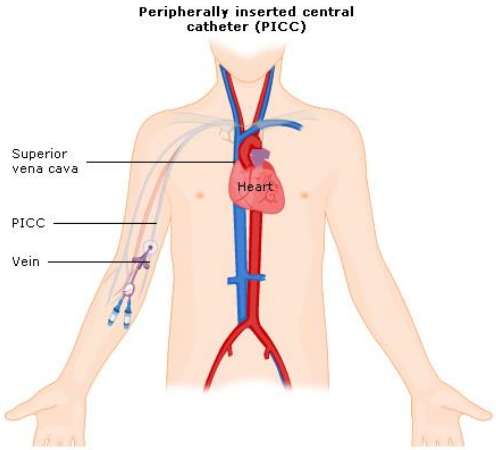


Implantable Port

An implantable port is a reservoir that sits under the skin. It is inserted into a vein in the neck with the tip placed at the junction of the superior vena cava/right atrium. The other end of the catheter is tunnelled into the skin which is attached to the reservoir and sits in a 'pocket' under the skin on the chest. In order to use the port for blood samples or medications a port needle needs to be inserted into the reservoir.



Peripherally Inserted Central Catheter



Peripherally Inserted Central Catheters (PICC) are inserted into a vein above or below the antecubital fossa, with the tip of the catheter placed at the junction of the superior vena cava/right atrium. They can be inserted using either a general or local anaesthetic.

PICCs come in different types and have different company names. Some of the common ones seen at GOSH are power PICC™s , Cook and Groshong®. However, this may be different in other hospitals and trust.

Some PICCs have clamps and those without clamps have internal valves. This is important to note, as this will change the way they are flushed at the end of infusions for some PTCs. This is explained in more detail in the flushing section.

Care of the tunnelled and non-tunnelled CVADs

Infection is the most common and serious complication associated with CVADs. To minimise infection risk, it is important that Aseptic Non-Touch Technique (ANTT) is always used when accessing the CVAD. The following section will explain the principles of ANTT.

The World Health Organisation's (WHO) '5 Moments of Hand Hygiene' (WHO, 2009) alongside local trusts ANTT guidance and policies should be adhered to at all times when accessing or caring for CVADs.

Aseptic Non-Touch Technique (ANTT)

The aim of **ANTT** is to minimise the introduction of micro-organisms, which may occur during preparation, administration and the delivery of IV therapy. The theory behind ANTT focuses on the basic principles of infection control, such as effective hand washing, the wearing of non-sterile gloves (in accordance with local hospital policy – GOSH do not wear gloves for ANTT unless there is a risk of exposure to blood or bodily fluids, or when preparing/administering cytotoxic/cytostatic medication)(Dougherty, 2000), maintaining asepsis of equipment and environment, and the use of alcohol based solutions for decontamination with adequate cleaning and natural evaporation of the alcohol. If alcohol-based products are not allowed to dry naturally, then the antibacterial properties of the agent will be ineffective, placing the patient at risk of developing an infection (Rowley et al 2010; RCN 2016.)

The EPIC 3 guidelines recommend that an aseptic non-touch technique (ANTT) must be used for catheter site care and for accessing the venous system (Loveday et al 2014).

Key Parts

- Key parts – the aseptic parts of the procedure include equipment that needs to have direct contact with aseptic key-parts of the patient, or any liquid infusion. If contaminated, key-parts provide a direct route for transmission of pathogens between the procedure and the patient (Rowley et al 2010).

- Key parts include:
    - Needles (any part of the actual needle itself and the inside of the sheath)
    - Syringe hubs
    - The end of the needle free access device

ANTT involves the essential practice of identifying, cleaning effectively and optimally protecting the key-parts during a procedure. For example, in IV therapy, syringe tips should always be protected by dedicated caps or the inside of syringe packets (Rowley et al 2010).

When cleaning an intravenous needle free access device, introduce the device into the centre of a large 70% alcohol/2% chlorhexidine impregnated wipe. Scrub the tip of the needle free access device hard generating friction for a minimum of 15 seconds and allow to dry for 30 seconds. The drying time is important as this is the time in which any existing bacteria is killed.

Assessing and maintaining patency

Patency of vascular access devices must be confirmed prior to use. The method and technique will vary according to the device and its location, and also organisational guidance. Please see the table below for guidance from the different PTCs.

GOSH	UCLH	RMH
Flush the device with 0.9% sodium chloride. Only withdraw blood for vesicant medications or when using a port-a-cath to confirm positioning.	For CVADs: Withdraw 9mls blood prior to flushing with 0.9% sodium chloride For PICCs: Withdraw 6mls discard blood prior to flushing with 0.9% sodium chloride	Flush the device with 0.9% sodium chloride. Withdraw 2-3mls of blood and give back if not taking blood samples.

Maintaining vascular access device patency is an important aspect in the care of devices. Maintaining patency prevents avoidable replacement of catheters caused by loss of function due to occlusion and it importantly prevents the mixing of incompatible medications and solutions in lumens (Capital Nurse)

Flushing

Vascular access devices must be flushed between each drug administration to prevent incompatibilities occurring and to maintain patency (RCN, 2014). The sections below will describe the different types of flushing techniques.

Pause-push technique

The most effective technique for flushing CVADs is the push - pause - flush technique. This technique generates turbulent flow in the lumen of catheters and helps to ensure the lumen is flushed clear and patency is maintained. It is advisable to use a syringe no smaller than 10ml to flush with, even if the flush volume required for the catheter is less than 10 ml. This is due to the risk of generating very high pressures with small syringes and damaging the CVAD. (Capital Nurse, 2020). The technique involves alternating between a brisk push of flush and a brief pause until the full flush volume has been administered.

Positive pressure

When flushing the CVAD after administration it is beneficial to use a 'positive pressure lock'. This is achieved by applying the line clamp while you are completing the final 2 ml of flush. Persistent withdrawal occlusion can often be prevented with positive pressure locking (Capital Nurse, 2023).

For CVAD's, Ports and open-ended PICC's, positive pressure is achieved by closing the clamp whilst flushing. For valved PICC's, some PTCs continue to flush the PICC, whilst removing the leur-slip syringe from the needle free access device and advise you not to use a leur-lock syringe for the final flush. Some PTCs, including UCLH, use BD MaxZero or MaxPlus connectors which automatically create positive pressure into the lumen when the syringe is disconnected from the connector.

The importance of syringe size

Syringe size has a significant impact on the risk of catheter damage. The basic principle is that smaller syringes generate higher internal pressures than larger syringes when flushing the device (Hadaway 2006). 10 ml syringes or larger will need to be used when first accessing and de-accesing any CVAD. Smaller syringes can be used once catheter patency has first been established using a 10 ml syringe (Hadaway 1998).

Heparin versus sodium chloride

There are currently two standard flushing solutions used most frequently on CVAD's. These are heparin and sodium chloride 0.9%. Low dose heparin flushes are frequently used to fill the lumens of a CVAD between use in an attempt to prevent thrombus formation and to prolong the duration of catheter patency. However, the efficacy of this practice is unproven (Bradford et al 2016; Molin et al 2014). Apheresis/haemodialysis catheters are commonly flushed with heparin 1,000-5,000 units per ml to maintain patency.

A rapid response report issued by the NPSA in April 2008 advised organisations to review local policies in order to minimise the use of heparin flush solutions for all vascular access devices (NPSA 2008) Since the publication of the National Patient Safety Agency Rapid Response Report (NPSA, 2008) highlighting the risks associated with heparin flushes, some NHS Trusts including UCLH and RMH have elected to stop using heparin to flush CVAD's, GOSH at time of editing this chapter still use heparin (Bravery, 2010).

Exit site care

Daily CVAD assessments:

- Insertion site assessment- look for any signs of infection, ooze, tracking
- Type of securement – sutures or mechanical device (if sutured, the hub must be sutured as well, not just the 'securing wings' as these often do not stop the CVAD slipping)
- Dressing assessment, intact or not, including the use of a chlorhexidine impregnated sponge or gel, which should be visible. If these are not used the actual insertion point should be visible
- Presence of needle free connectors
- Presence of non-coring port access needle
- For PICCs – external length visible (Capital nurse)
- Always use ANTT for exit site care.

Cleaning:

- Clean site at dressing changes using 2% chlorhexidine in 70% isopropyl alcohol solution (Chloraprep). For GOSH patients hold on the exit site for 10 seconds and then a further 20 seconds back and forth with friction. Allow to dry naturally. For RMH clean back and forth with friction. If patient is UCLH please consult them for their local policy.
- If there is loose blood or exudate present, this should be removed first using sterile gauze and 0.9% sodium chloride rather than the chloraprep.
- If there is blood or exudate on the actual line clean this with sterile gauze and sodium chloride wiping away from the exit site.
- With PICCs, ensure the skin under the securAcath is cleaned.

Dressing CVADs

Sterile semi-permeable transparent dressing e.g. IV3000 are recommended, although some trusts local policies may differ. For example, UCLH use Tegaderm with chlorhexidine gel pad (Tegaderm CHG). Whichever dressing of choice, it should be changed every 7 days (or sooner if dressing becomes wet, soiled or detached).

Anti-microbial dressings

Antimicrobial dressings such as BioPatch ® or Tegaderm CHG can be used if supported by the PTC. **Biopatch®** steadily release chlorhexidine gluconate (CHG) over 7 days. There is evidence to show they reduce the rate of central line infections by up to 69% (Timsett et al 2009). Some trusts utilise these, whereas others utilise different dressings. Please follow local policy.
Great Ormond Street use Biopatches®:

- First 12 weeks post line insertion for CVADs
- If patient is colonised with MRSA, then for duration of timeline in-situ

Alternative antiseptic solutions that may be used if chloraprep is not tolerated:

- Providone-iodine 10% (alcohol version)
- 0.5% chlorhexidine gluconate in 70% denatured ethanol B – short term use only

Bathing, showering and swimming

Bathing and showering:

If the patient wishes to have a bath, he/she should be advised to keep the exit site out of the water and not to let the catheter ends hang in the bath water, even if it is covered with an occlusive dressing.
If the patient is using an IV dedicated transparent dressing, then there is no need to change the dressing after bathing and showering, as long as the dressing remains occlusive, and no water has seeped underneath the dressing.

Swimming

Swimming is not permitted with central lines, however, is possible with patients with a de-accessed port.

Troubleshooting

Occlusions

Withdrawal Occlusion or Total Occlusion may be due to one of the following:

- Catheter tip malposition
- Intraluminal clot
- Intraluminal medication precipitate
- Catheter kink (external and internal to body)
- “Pinch-off”
- Catheter related thrombosis (intra and extraluminal)
- Suture constriction
- Fibrin sheath/tail/flap
- Malposition/dislodgement of implanted port needle
- Fibrin in port reservoir
- Other

Withdrawal occlusion

If the CVAD will not withdraw (sample blood) give urokinase. Some PTCs require you to be trained to do so, so follow trust policy.

Total occlusion

If the CVAD is blocked i.e. it will not infuse or aspirate, please contact the PTC supervising the child's care. Do not attempt to unblock totally occluded catheters unless trained to do so. N.B. Risk of catheter rupture, catheter embolus

Catheter damage

The child will need referral to the PTC supervising the child's care for catheter repair unless repair kit is available locally and local staff are trained and experienced to repair the catheter.

Action

- For trusts which provide line safety packs, clamp the catheter between the patient and the damaged area with a smooth-edged, atraumatic clamp (use 2 clamps if possible). Place gauze underneath the clamps to prevent further damage to the line. UCLH do not provide line safety packs and recommend folding the catheter back on itself using an elastic band.

- Seal damaged area with a sterile occlusive dressing.

- Repair catheter (Only if trained to do so)

- Take cultures from all lumens after repair.

- Ensure the child/young person/parents are familiar with the clamping/taping procedure if damage should occur at home.

Protocol / Standard Operating Procedure (SOP) for Urokinase administration (if appropriate, use alteplase or alternatives as per local policies & protocols)

Urokinase is a thrombolytic agent which converts plasminogen into plasmin (fibrinolysin) a proteolytic enzyme that breaks down fibrin as well fibrinogen and other plasma proteins. Due to national shortages of alteplase and forms of Urokinase at the time of editing this chapter, many PTCs are using Taurlock ®. This section will provide guidance on its use.
Each box of Taurolock™-U25.000 contains: Taurolock (taurolidine and citrate 4%) 5mL ampoule PLUS Urokinase 25,000 units powder for reconstitution vial. TauroLock™-U25.000 must be stored between 15 – 25 °C.

GOSH recommendations for dosing information for the management of withdrawal, partial and total occlusions:
Urokinase is available as Urokinase 25,000 units per vial. When reconstituted with 5ml of 0.9% sodium chloride the final concentration is 5,000units/ml.

UROKINASE ADMINISTRATION VOLUMES FOR THE MANAGEMENT OF WITHDRAWAL/PARTIAL/TOTAL OCCLUSION

Urokinase is available as Urokinase 25,000 units per vial. When reconstituted with 5ml of 0.9% sodium chloride the final concentration is **5,000units/ml**

CENTRAL VENOUS ACCESS DEVICE	DOSE OF UROKINASE to administer
PICC non cuffed & cuffed (e.g MedComp Vascu-Line, MedComp Pro PICC, power-injectable PICC) 3Fr 4Fr single or double 5Fr single or double	 Give 2500units (0.5mls) Give 2500units (0.5mls) down each required lumen Give 2500units 0.5mg (0.5mls) down each required lumen
Tunnelled non-cuffed CVC(e.g MedComp PICC, MedComp ProPICC, power-injectable PICC) 3Fr 4Fr single or double 5Fr single or double	 Give 2500units (0.5mls) Give 2500units (0.5mls) down each required lumen Give 2500units (0.5mls) down each required lumen
Single lumen tunnelled cuffed CVC (e.g Broviac®/Vygon LifeCath/PowerLine™) 2.7Fr/4.2Fr/5Fr/6.5Fr/6.6Fr	Give 2500units (0.5mls)
Single lumen tunnelled cuffed CVC (Hickman®) 9.6Fr	Give 5000units (1ml)
Dual lumen tunnelled cuffed CVC (e.g. MedComp Vascu-Line) used for babies/infant 4Fr & 5Fr	Give 2500units (0.5ml) down each required lumen
Dual lumen tunnelled cuffed CVC (e.g. Hickman®/Vygon LifeCath/Pro-Lines®/PowerLine™) used for older children, hence longer length & larger volume 5Fr/6Fr/7Fr/9Fr/10Fr	Give 5000units (1ml) down each required lumen
Triple lumen tunnelled cuffed CVC (e.g. Hickman®) 10Fr/12Fr	Give 5000units (1ml) down each required lumen
Implantable Port: Multiple different brands Low Profile (small) Large	 Give 5000units (1ml) Give 7500units (1.5mls)
Central venous access (temporary) for extracorporeal therapies (Gamcath®/Vascath®) catheter Various sizes	The amount instilled must be the equivalent of the volume of the dead space of the catheter The priming volumes for the catheter are printed on the catheter or clamps
Central venous access (permanent/cuffed) for extracorporeal therapies (Kimal SpiltCath®/Gambro/Tyco/Permcath®)catheter Various sizes	The amount instilled must be the equivalent of the volume of the dead space of the catheter The priming volumes for the catheter are printed on the catheter or clamps
Short term CVCs used mainly with the ICUs and post surgical wards - As per ICU guideline 'Initiative to increase CVL durability on intensive care units & post surgical wards'	The amount instilled must be the equivalent of the volume of the dead space of the catheter. Some catheters will have the volumes printed on the lumen.

Administration details:

Only the urokinase powder in the vial is to be used, the Taurolock ampoule must be discarded. The recommended reconstitution volume for Urokinase 25,000 units is 5mL of 0.9% sodium chloride.

- Reconstitute urokinase powder with 5mL of 0.9% sodium chloride resulting in a final concentration of 5000units/ml
- The reconstituted solution must be used immediately
- Each dose of urokinase will need to be instilled & left within the CVAD for 2 hours
- Urokinase should be aspirated/withdrawn from all CVAD prior to flushing, however where aspiration of urokinase/bloods fails, urokinase can be flushed in.
- A second dose will be required if the occlusion is still present after flushing.

Caution should be exercised with patients who have thrombocytopenia or other haemostatic defects. At GOSH, a platelet level of 50 × 109/L or above is recommended prior to the administration of urokinase. In cases where a platelet level of greater than 50 × 109/L is not feasible; this needs to be discussed with the clinical team and used as required.
Never leave a total occluded CVC unresolved.

Adverse effects:

Please refer to manufacturer guidelines/BNFC/Summary of Product Characteristics (SPC).

Cautions:

For patient undergoing surgery within 24 hours, please discuss with your clinical team prior to administration of urokinase.

Contraindications:

Urokinase is contraindicated for patients with a known allergy to urokinase or when a patient is currently taking medication with known adverse interaction to urokinase.

Three-way tap method

Using a Thrombolytic in a Completely Blocked Catheter using a 3-way tap

- Attach 3-way tap and syringes. 3-way taps are now contraindicated for routine IV use but are still recommended for this procedure. Always use a 3-way tap without an extension set
- Open clamp if there is one
- Open stopcock to the empty syringe and the blocked catheter
- Pull back on the plunger of the empty syringe to create a vacuum in the catheter. You will need to pull quite forcibly
- Maintain suction with one hand and with the other hand turn stopcock so it is closed to the empty syringe and open to the syringe containing thrombolytic, which will be sucked into the catheter. Don't worry if it seems that very little thrombolytic is sucked in: even a tiny volume will reach several cm into the catheter.
- Leave for several hours or overnight. Do not clamp catheter as this will prevent the thrombolytic from penetrating into the line
- After this time, assess the catheter by attempting to flush it with 0.9% sodium chloride in a 10 ml syringe. Do not use excessive force. It is best not to try aspirating before flushing at this stage as you may block the catheter again.
- If the catheter is still completely blocked, repeat the procedure: sometimes you will need to repeat it several times before it works. Sometimes leaving the thrombolytic in overnight seems to help.
- Once the catheter can be flushed, and only then, check for flashback.

References

- Higher Education England (2022)
- Royal College Nursing
- World Health Organisation (WHO) (2009) *Hand Hygiene Technical Reference Manual: to be used by health care workers, trainers and observers of hand hygiene practices.* WHO: Geneva

8.

EXTRAVASATION

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8. Extravasation

All Trusts should have a local extravasation policy which should be followed.

If a PTC or POSCU has a robust referral pathway for any extravasation injury, then this should be followed at all times.

For those POSCU's whose plastics team is off site, and the referral pathway is not robust in terms of treating paediatric oncology patients (i.e. ability to access Portacath's, no haem/onc speciality), please discuss with the PTC Haematology or Oncology Registrar for advice. This should be done immediately and must not cause a delay in the treatment of the extravasation injury.
If it would be more appropriate for the patient to be seen by the Plastics Team at the PTC, then the PTC Registrar will facilitate this.

All extravasation or suspected extravasation injuries should be reported to the patient's PTC.

All staff involved in the administration of chemotherapy must be fully trained and aware of local Trust policies.

What is Extravasation?

Extravasation is the inadvertent leakage of a vesicant solution from its intended vascular pathway (vein) into the surrounding tissue (Infusion Nurses Society, 2006; European Oncology Nursing Society, 2007; Dougherty and Lister 2008; Doellman et al, 2009; Royal College of Nursing, 2009).

A vesicant refers to any medicine or fluid with the potential to cause blisters, severe tissue injury (skin/tendons/muscle) or necrosis if it escapes from the intended venous pathway (Sauerland *et al*, 2006; Hadaway, 2007; Doellman *et al*, 2009).

The degree of injury ranges from mild skin reaction to severe necrosis (European Oncology Nursing Society, 2007).

In severe cases extravasation injury may lead to amputation (Roth, 2006; Hadaway, 2007; Doellman et al, 2009).

There has been little research into extravasation (due to ethical considerations limiting controlled research) and most evidence is based on small, uncontrolled trials or case reports (Hadaway, 2007; Doellman et al, 2009).

A PLASTIC SURGEON REFERRAL SHOULD BE SOUGHT IMMEDIATELY WHERE LARGE VOLUMES OF INFILTRATE HAVE ACCUMULATED.

Infiltration

Infiltration is the inadvertent leakage of a non-vesicant solution from its intended vascular pathway (vein) into the surrounding tissue (Infusion Nurses Society, 2006; European Oncology Nursing Society 2007; Dougherty and Lister 2008; Doellman et al. 2009; Royal College of Nursing 2009).

Infiltration is increasingly seen as a benign event as it generally does not lead to tissue necrosis; however, a large volume of infiltrate can cause compression of nerves and acute limb compartment syndrome (ALCS) resulting in long term disability (Roth, 2006; Doellman et al, 2009).

If this is the case then surgical intervention e.g., fasciotomy may be required to prevent nerve compression and compromise of arterial circulation (Hadaway, 2007).

Flare

Flare is a local inflammatory reaction characterised by local erythema, venous streaking and pruritus along the injected vein. This is distinguishable from extravasation by the absence of pain and swelling and the presence of a blood return.

Vein irritation is seen as erythema or dark discolouration along the blood vessel with aching and tightness. **Neither of these two scenarios is considered an extravasation.**

Vesicant drugs and solutions reported to cause extravasation injury:

Antimicrobials	Vasocompressive agents
• Penicillin • Vancomycin • Aciclovir, Ganciclovir • Gentamicin • Nafcillin • Amphotericin • Cefotaxime	• Dobutamine • Dopamine • Epinephrine (Adrenaline) • Norepinephrine (Noradrenaline) • Vasopressin
Concentrated electrolyte solutions	**Cytotoxic agents**
• Calcium chloride 5.5% • Calcium gluconate 10% • Potassium chloride 7.45% • Sodium bicarbonate 4.2% or 8.4% • Sodium chloride 10%	• Cisplatin • Dactinomycin • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin • Mechlorethamine • Melphalan • Mitomycin • Paclitaxel • Vinblastine • Vincristine • Vinorelbine • Vindesine
Hyperosmolar agents	**Other**
• Total parenteral nutrition • > 10% dextrose • Mannitol 15% • Phenytoin	• Radiographic contrast media • Promethazine (phenergan) • Diazepam • Digoxin

Sauerland (2006), Hadaway (2007), Dougherty (2008).

This is not an exhaustive list; there are many more.

Risk factors for infiltration and extravasation

Risk factors include device related, drug related, patient related, and clinician related (Sauerland et al. 2006). See table below

Device related

Peripheral cannula

- Metal/steel needles (butterfly)
- Large gauge cannula relative to vein size
- Inadequately secured cannula
- Undesirable cannula site location (e.g. antecubital fossa, dorsum of hand or wrist rather than forearm, areas of joint flexion and use of dominant hand)
- Clot formation above cannula site

Central venous access device (CVAD)

- CVAD placed in an area prone to movement; difficult to secure
- Inadequately secured needle in implanted port
- Inadequately secured catheter
- Inappropriate needle length for Portacath (i.e. too short to reach back of reservoir)
- Development of fibrin sheath at catheter tip
- Portacath / catheter separation, catheter fracture or catheter dislodgement
- Flushing with a small gauge syringe

Drug related

- Vesicant potential
- Volume of drug/fluid infiltrated
- Concentration of vesicant drug/fluid
- Repeated use of the same vein for vesicant administration
- pH of drug/fluid (extremes of pH i.e. acid or alkaline - pH < 5 or >9)
- Osmolarity of drug/fluid (osmolarity can influence the degree of tissue damage e.g. hypertonic drugs/solutions e.g. 10% Dextrose and parenteral nutrition solutions)
- Vasoconstrictive potential (extravasation of vasoconstrictive substances e.g. dobutamine, dopamine, epinephrine, norepinephrine and vasopressin can cause ischaemic necrosis)
- Cytotoxicity (drugs that bind to DNA can cause greater damage and may remain in the tissues causing further damage)

Patient related

- Age (very young or old)

• Patients with small, fragile or thrombosed veins • Impaired communication - unable to communicate due to young age or confusion, sedation, inability to speak or language issues • Compromised circulation • Altered sensory perception • Poor understanding of risk related to anxiety or fear, cultural barriers, or medicines • Active patient • Lymphoedema
Clinician related
• Lack of knowledge • Lack of intravenous therapy skills • Unfamiliarity with CVAD use and management • Interruptions or distractions during medication administration

(Sauerland et al, 2006; Dougherty 2008; Doellman et al, 2009)

Recognition of infiltration / extravasation

It is important for the nurse to be able to recognise the early signs and symptoms of infiltration and extravasation (Dougherty, 2008). See Table below.

Infiltration	Extravasation
• Coolness or blanching at the cannula insertion site • Swelling • Tenderness/discomfort • Taut or stretched skin • Leakage of fluid at the insertion site • Inability to obtain blood return (not always present) • Change in quality and flow of the infusion or injection • Numbness, tingling or "pins and needles"	As for infiltration, plus: • Burning, stinging pain • Redness may occur followed by blistering, tissue necrosis and ulceration

(Hadaway, 2007; Dougherty, 2008)

Prevention of infiltration/extravasation

Device related:

Peripheral IV access

- Place cannula in muscled area in forearm when possible
- Use the smallest gauge plastic cannula feasible
- Avoid joints (e.g. wrist, antecubital) and limbs with impaired arterial, venous or lymphatic circulation
- Stabilise & secure the cannula in place using dressing that does not obscure the site (i.e. transparent)
- Confirm blood return prior to vesicant administration

Central IV access

- Preferred route of administration
- Confirm blood return prior to vesicant administration
- Portacath: ascertain correct needle placement in septum
- Portacath: stabilise & secure the needle in place using dressing that does not obscure the site (i.e. transparent)
- If catheter tip is questionable, assess prior to vesicant administration (i.e. through a CXR)

Patient related:

- Instruct the patient & family about the risks of vesicant administration
- Instruct the patient & family to notify a health care professional if the child/young person experiences any pain/burning/change in sensation at the cannula or port site; this includes non-verbal assessment also
- Instruct the patient & family not to disturb or dislodge the cannula or port needle and to take care when mobilising
- The patient & family should be able to understand these points

(Sauerland et al, 2006)

Nursing responsibilities when administering intravenous medicines

Intravenous therapy is now an integral part of the majority of nurses' professional practice (RCN, 2009). Any nurse involved in the administration of intravenous therapies must be competent to undertake the procedure and act in accordance with the NMC Code and maintain knowledge and skills (NMC, 2008a).

The nurse has a duty of care to the patient to monitor the patient and their response throughout the duration of intravenous medication administration (RCN, 2009; NMC, 2008b).

The Trust medication policy must be adhered to when administering intravenous medications and fluids. Any member of nursing staff deemed competent in IV therapy may administer a non-cytotoxic vesicant drug or infusion via peripheral and central venous access devices. However, the nurse must undertake all safety precautions and assessments and close monitoring **must** be continued throughout the infusion.

Only staff deemed competent to administer cytotoxic medication may administer a cytotoxic vesicant drug or infusion via peripheral and central venous access devices.

Monitoring of the infusion

The access device should be well secured (Sauerland et al, 2006; Dougherty, 2008)

The pressure of the infusion pump **must** be monitored & documented at least hourly, along with the signature of the person doing so, on the child's fluid chart.

The infusion site **must** be inspected every 30-60 minutes and documented when in use and if extravasation or infiltration is suspected (Masoorli, 2003).

The port needle entry site should be observed before administering vesicants or irritant solutions (Sauerland, 2006).

The suggested maximum pressure alarm setting for an infusion pump is 15–25mmHg for vesicant drugs.

More frequent checks may be necessary in some instances depending on the patient, infusate, vascular integrity and the vascular access device being used (15–30 minutes).

The pressure alarm limit **must** be set when a vesicant infusion is commenced & rechecked at the beginning of each shift, if still running.

Record pump pressures and site monitoring on the fluid balance charts as per hospital policy.

A rise in pressure **must** be investigated.

The pressure reading should not be the sole indicator for an extravasation (Sauerland et al, 2006).

Bandages are not recommended for use when administering bolus vesicant therapy and should be used with caution for infusions. **Never** cover the insertion site as these compromises effective monitoring (Roth, 2006; EONS, 2007).

Patient & family queries about pain, discomfort or swelling must be investigated; they should also have been informed of signs and symptoms (Sauerland et al, 2006)

Management of infiltration and extravasation

Early intervention and identification of the first signs and symptoms of infiltration and extravasation is crucial, in order to prevent serious adverse outcomes (Doellman, 2009).

Compliance with guidelines is essential to minimise the complications associated with extravasation or infiltration (Roth, 2006).

THIS IS A MEDICAL EMERGENCY ANYTIME OF THE DAY OR NIGHT

The recommended immediate management is

- Immediately stop the infusion/injection (Doellman et al 2009)
- Explain the procedure to the child & family.
- Aspirate as much of the residual drug as possible (to minimise the injury caused by the residue of the drug
- **Under no circumstances should the device be flushed.**
- Leave the cannula/port needle in situ (in case plastic surgeon wants to use to facilitate treatment and administration of any antidote(s)).
- Mark the extravasated area with a soft tipped pen.
- Disconnect administration set or syringe containing drug but retain it to determine amount of drug extravasated/infiltrated.

Subsequent Action

This may include:

- **Monitoring** – the site will be observed, elevated and monitored to determine whether further treatment is required.
- **Conservative management** – this may involve the use of hot or cold compresses or antidotes (if possible).
- **Surgical management**– this involves a saline washout, a procedure that dilutes the extravasated drug in the tissue (Wickham *et al*, 2006). The "Flush Out" technique should only be performed by an experienced member of staff.

Further management as indicated

The team should prescribe pain relief as required.

Administer analgesia as required/prescribed.

If a limb is affected, it should be elevated.

For All Vesicant Cytotoxic Drugs: Early referral to a Plastic Surgeon should be considered.
Any extravasation injury that occurs in a POSCU must be discussed with the PTC Registrar who will then discuss with the PTC plastic's Team. If the patient needs to be seen by the Plastics Team, then the PTC Registrar will facilitate this.

Document the incident and any actions taken in the child's health care records and complete an incident form.

Inform child & family of the following:

- That an extravasation is suspected/has occurred
- The possible cause of the extravasation
- What action / treatment will be required
- Any follow-up arrangements
- That an incident form will be completed
- Allow time for any questions and/or queries

Documentation of the process is essential if litigation were to occur (Masoorli, 2003; Roth, 2006). This

documentation will be done by nurses and doctors.

In accordance with the NMC (2009) record keeping is not an option it is an integral part of nursing and is

essential to the provision of safe and effective care.

Extravasation Kit

Extravasation kits should be available in all areas where vesicant drugs are administered. Contents of kits vary from Trust to Trust; however the basic contents may include:

- Hyaluronidase
- Lidocaine
- Scalpel blade
- Sterile field
- Normal giving set
- 500 ml bag of sodium chloride 0.9%
- Blunt large bore needle
- Syringes of varying size
- Needles of varying size
- Sterile gauze
- Jelonet dressing
- Paraffin gauze packs
- Extravasation Policy
- Extravasation documentation forms

Saline washouts (Flush out Technique)

The flush out technique should only be performed by a trained member of staff. Good results have been achieved with this technique when used at an early stage with adults & children.

It should be initiated as soon as possible following the extravasation injury and must be performed within 12 hours. For young people and children, ideally, they should be taken to theatres for the flush out technique. If this is not possible then adequate analgesia must be administered or sedation where appropriate. The age of the child & the extent of the injury will determine if a local or general anaesthetic will be required.

Antibiotic prophylaxis may be recommended in some patients depending on the severity.

In a saline washout the injured area is:

- Injected with the enzyme hyaluronidase into the subcutaneous tissues under the area of damaged skin
- Peripheral incisions are made around the “clock face” of the injury
- Using an atraumatic cannula the area is perfused with 0.9% sodium chloride
- Fluid entering through the needle should flow freely through the stab incisions. Excess fluid can also be massaged out of the tissues by gentle manipulation.
- The washout efflux may be tested for decreasing concentrations of toxin
- Dressing applied post-operatively and the limb elevated for 24 hours

(Gault, 1993)

Follow up treatment

If the plastic surgery team have been involved, follow their management plan, if not, follow the plan from the child's/young person's medical team.

Further surgical intervention may be required.

The child/young person may need their injury to be reviewed as an outpatient.

If no action is required observe the extravasation site for:

- *Colour*
- *Sensitivity*
- *Swelling*

This should be done as often as required by the condition of the child/young person until the site regains its normal appearance.

If limb involvement, elevate it (if appropriate, monitor the limb mobility of the child/young person).

If the extravasation site deteriorates or its condition does not improve another referral **must** be made to the Plastic Surgery Team.

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9.

NUTRITION INTERVENTION IN PAEDIATRIC ONCOLOGY & HAEMATOLOGY PATIENTS

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9. Nutrition intervention in Paediatric Oncology & Haematology Patients

The promotion and maintenance of good nutritional status is an important part of the supportive care for patients undergoing treatment. Well-nourished patients are thought to better tolerate their treatment (1,2). As treatment protocols are refined and prognosis improves, we are now also dealing with nutritional issues such as obesity and long-term disturbance in eating patterns.

The aims of nutritional support in paediatric oncology patients are

- To reverse malnutrition seen at diagnosis by involvement with the patient and family as soon as possible.
- To promote/maintain normal growth and development.
- To prevent nutritional depletion/malnutrition associated with treatment.
- To meet the needs for increased demands for nutrients during treatment.
- To aim to decrease the incidence of infection by supporting return to immune competence
- To maintain gut function and gut wall integrity

Causes of nutritional problems in oncology patients

- Loss of appetite
- Nausea / Vomiting (including anticipatory vomiting)
- Sore throat/mouth
- Taste changes/ loss of taste
- Pain/Fatigue
- Dry mouth/ reduced secretions
- Malabsorption/ Diarrhoea
- Intermittent constipation
- Metabolic disturbances
- Food aversion/ Behavioural issues associated with food / Psychological factors
- Steroid therapy

Nutritional screening and referral

Nutritional screening is essential to identify patients who are already or at risk of becoming malnourished (NICE, 2006). The child's height and weight should ideally be documented in the medical notes at the initial medical consultation and plotted on the appropriate RCPCH UK-WHO growth charts. Any weight loss should also be documented as a percentage weight loss. Further nutritional screening should be undertaken on initial admission to the ward and weekly thereafter, using a locally agreed nutrition screening tool (e.g., STAMP/NST/PYMS/ SCAN).

Patients identified as being malnourished or 'at risk of becoming malnourished' should be referred to a dietitian as indicated by the locally agreed screening tool/growth chart/percentage weight loss.

Children identified as being "at risk" of malnutrition or malnourished

Children identified as being "at risk" should have a full nutritional assessment by a dietitian. This should include documentation in the medical notes of:

- Anthropometrical measurements:
  - Weight* and height (and the growth chart centiles)
  - Identification of percentage weight loss/centile reductions
  - MUAC (mid upper arm circumference) where available
- Biochemical data for signs of any micronutrient deficiencies (e.g., Vitamin D, hydration status, and to monitor for re-feeding syndrome)
- Clinical information including signs and symptoms such as diarrhoea, nausea and vomiting, mucositis, taste changes, constipation, and relevant medications that may impact nutritional status.
- Dietary history including qualitative /quantitative information utilising food record charts and verbal information gathered from the child and their carers.
- Estimation of energy, protein, and fluid requirements (3)
- A clear plan of action with realistic goals agreed with the medical, nursing and other HCPs, and most importantly the patient, and the carer.

*Tumour mass/ ascites/oedema need to be considered in these measurements

Nutritional strategies

May include any or a combination of the following:

- Maximizing oral intake through food fortification and the addition of nutritional supplements and sip feeds
- Enteral tube feeding
- Parenteral nutrition (PN)

Oral Intake

The reasons for possible suboptimal intake may be multifactorial. It is important to optimise symptom management and maximise the nutritional quality of any food eaten. Advice can be given on increasing energy and protein. Copies of a patient /parent information booklet '**Helping your child to eat during cancer treatment'** are available from the CCLG (4) and online and provides information on managing dietary-related side effects of treatment. Referral to the local dietitian should be made as soon as nutritional challenges or changes in nutritional status are identified.

Foods to avoid

Immunocompromised patients are at increased risk of developing severe complications because of foodborne infection. Patients and their families should be advised to follow good food hygiene practices and encouraged to make wise choices when eating outside the home e.g., promote the use of the Food Standard's Agency 'Scores on the doors' App.

As a minimum, the NHS and Food Standard's Agency recommended that patients receiving chemotherapy should avoid the following (5, 6)

Eggs:

Avoid Raw or lightly cooked eggs. Patients **can** have well cooked eggs with the 'Lion Mark'.

Dairy Products:

Avoid unpasteurised cow's milk, goat's milk, sheep's milk, or cream and other food products made with this milk.

Avoid pasteurised or unpasteurised mould ripened soft cheese with a white coating on the outside such as Brie, camembert or chevre or soft blue chesses such as Danish blue, gorgonzola and Roquefort (UNLESS cooked until steaming hot)

Patients **can** eat:

- pasteurised or unpasteurised hard cheeses such as cheddar, gruyere, parmesan
- pasteurised semi-hard cheeses such as edam and stilton.
- Pasteurised soft cheese such as cottage cheese, cream cheese, mozzarella, feta, paneer, ricotta, cheese triangles and halloumi
- Pasteurised yoghurt cream and ice cream

Meat

Avoid

- Pâté
- Raw and undercooked meat

Fish

Avoid

- Raw shellfish (well-cooked shellfish are safe to eat)
- Uncooked smoked fish such as smoked salmon or raw fish sushi should be avoided due to a listeria outbreak linked to smoked fish. Patients should only eat smoked fish products that have been thoroughly cooked and are steaming hot all the way through (5)

Patients should be encouraged to eat fruit and vegetables and do not need to peel them or wash in salted water etc.

Nutritional Supplements & Sip feeds

Refer to the local dietitian for advice and guidance on locally available products and their suitability. When nutrition related problems are identified at the PTC, the patient will be reviewed there and commenced on an appropriate supplement regimen. In complex cases, or where no local dietitian is available to consult, please discuss with PTC dietitian.
These products can be useful in patients who are maintaining some oral intake, but do not require enteral feeding

Table 9.1 Examples of nutritional supplements (prescription only) *

Types of supplements	Examples
Energy & Protein supplements (not nutritionally complete) (milkshake type drinks)	Scandishake / Calshake / Enshake / Aymes shake / Foodlink Complete / Complanshake (**Care must be taken when using these products with younger children: seek advice from the dietitian**)
Sip Feeds (not nutritionally complete) (juice type drinks)	Paediasure Plus juice For older children (e.g., 8+, over 30kg): Provide extra, Ensure plus juice style, Fortijuce
Sip Feeds (nutritionally complete). Milk-type products, available in a range of flavours.	Paediasure / Fortini/ Frebini Fortini compact and Paediasure compact are concentrated, lower volume versions of the above For older children (8+): Fortisip, Fortisip compact Ensure Plus, Ensure Compact, Fresubin Energy, Aymes2cal, Altraplen
Energy Supplements	Glucose Polymers, Maxijul / Polycal / Vitajoule Fat emulsions (Calogen, Liquigen), Procal shot and Procal powder Combined fat and glucose (Duocal) Fortified energy products e.g., Calogen extra, Altrashot, (**These products should only be prescribed with instructions**

	for use provided by the dietitian)
Specialist Oral Nutritional Products	Aymes ActaSolve -Vegan nutritional supplement

*Not an exhaustive list
Always check suitability for patients following a halal or kosher diet and consult allergen list

Enteral Feeding

Enteral feeding should be considered if there is a reduction of appetite and loss of weight, despite offering supplements or where this reduction in appetite is likely to continue for more than one week. Appropriate and timely placement of an enteral feeding tube may ultimately reduce stress for both patients and carers, as it allows for the provision of nutrition support as well as a route for the administration of medicines and water. However it is also necessary to guard against feeding tube dependency.
Indications for Enteral feeding:

- ≥10% weight loss on admission, not able to take nutritional supplements and have poor food intake
- Meeting <50% of estimated energy/protein requirements
- Unable to maintain growth on current oral intake
- Tumour type with lower threshold for instigating enteral feeding :
    - Nasopharyngeal tumours
    - Neuroblastoma
    - AML
    - Burkitt's lymphoma
    - Hepatoblastoma
- , Other indications for Enteral feeding
    - Patients with a large tumour mass may require early enteral feeding, despite presenting with no apparent weight loss e.g., Wilm's tumour
    - Younger patients are more likely to require enteral feeding or insertion of nasogastric feeding tube for administration of medication and/or fluid
    - Patients where the tumour mass impacts on the ability to eat or drink e.g. patients with disease affecting head and neck area should be considered for early instigation of nutrition support.

Contraindication for Enteral feeding: ideally supplementary enteral feeding should be avoided in these patient groups

- ALL (low risk)
- Patients presenting with weight loss following steroid associated weight gain (after cessation of steroids)

Enteral feeds can be administered via nasogastric tube or gastrostomy tube. Ideally any nasogastric tubes that are placed should be of the longer lasting polyurethane / silicone type to minimise localised tissue trauma and psychological distress associated with repeated tube replacement. Nasogastric tube insertion may be contraindicated in patients with nasopharyngeal disease.

Placement of a gastrostomy should be considered in patients expected to have lengthy treatment regimens which impact on appetite e.g., those undergoing treatment for medulloblastoma following the

PNET5 chemotherapy regimen, patients with nasopharyngeal tumours, high risk osteosarcoma patients. Gastrostomy tube placement is usually contraindicated in patients with extensive abdominal disease.

Post-pyloric feeding (naso-jejunal tube/gastrostomy with jejunal extension/jejunostomy) should be considered for children with gastric dysmotility, acute pancreatitis, severe vomiting, or high risk of aspiration. It is worth noting that jejunal feeds require near continuous feeding and bolus feeding is contraindicated in this group.

The main advantage of enteral feeding is that the parents can be taught to administer feeds at home. Ready-made preparations for enteral feeding are commercially available and can meet the specific requirements of the child. The feed is introduced gradually, and the child assessed in terms of tolerance regarding diarrhoea, nausea, or vomiting. In some cases, the feed may be given in the evening (although rarely overnight in the home environment), which allows the child to take part in normal activities and encourage oral intake during the day.

Patients receiving enteral feeds should be referred to the dietitian for full nutritional assessment and to devise an age and treatment appropriate feeding regimen. The dietitian will also be able to make feed recommendations based on the patient's cultural and religious requirements. Most patients will also need an enteral feeding pump and ancillary equipment for use at home. Parents/carers need to be trained in the use of this equipment and the testing of the position of a nasogastric feeding tube when necessary (see local policies on assessing parental competency).

Table 9.2 Types of Enteral Feeds*

Feed	Age (Weight)	Indication
Paediasure (1kcal/ml) Nutrini (1kcal/ml) Paediasure Plus (1.5 kcal/ml) Nutrini Energy (1.5 kcal/ml)	1 – 10 yrs. (8-30kg) 1 – 6 yrs (8-30kg) 1 – 10 yrs (8-30kg) 1 – 6 yrs (8-30kg)	Feed suitable as an enteral feed
Ensure (1.0 kcal/ml) Tentrini (1kcal/ml) Tentrini Energy (1.5kcal/ml) Jevity Plus (1.2 kcal/ml)	>6 years 7-12yrs (21-45kg) 7-12yrs (21-45kg)	Feed suitable as an enteral feed
Osmolite (1.0kcal/ml) Nutrison (1.0kcal/ml) Fresubin Original (1.0kcal/ml) Osmolite plus (1.2kcal/ml) Osmolite 1.5 (1.5kcal/ml) Jevity (1.1kcal/ml) Jevity1.5 (1.5kcal/ml) Nutrison Energy (1.5kcal/ml) Fresubin Energy(1.5kcal/ml)	> 12 yrs (>45kg)**	As above for the older child

*Not an exhaustive list

** Abbott feeds e.g. osmolite and jevity can be used in patients over 30kg if appropriate for the individual patient

In cases of severe diarrhoea or suspected malabsorption, a specialist hydrolysate feed should be considered; examples of such feeds can be found in Table 3. Consult the dietitian for guidance on the feed that best suits the patient.

Table 9.3 Semi elemental/ elemental/peptide-based feeds*

Feed	Age (weight)	Nutritional aspects
Pepti junior Pepdite Pepdite 1+ Infitrini Nutrini peptisorb SMA Althera Similac Alimentum Nutrini peptisorb energy Peptamen junior Peptamen Junior Advance Nutrison Peptisorb Advanced Paediasure Peptide Perative Vital 1.5 Nutrison Peptisorb Advanced High Energy, high Protein	<1 year<1 year>1 year <1 year >1 year >1 year >1 year <1 year 1-6 years (8-20Kg) >10 years 1-10 years >10 years > 10years >10 years >10 years >10 years	Semi-elemental, peptide-based feeds. Variable fat composition and content
Neocate LCP Neocate Junior Elemental 028 SMA Alfamino Elecare (Abbot) Puramino	<1 year >1 year -10 years > 1year < 1 year <1 year < 1 year	Amino acid based 'elemental feeds'

*Not an exhaustive list
Always check suitability for patients following a halal or kosher diet and consider allergen list.
Hydrolysate feeds, e.g. Pepdite 1+ and Pregestimil should be considered before using elemental feeds.

Blended Diets /Food based Enteral feeds:
Increasingly, parents/carers are looking towards blended enteral feeding diets as a means of providing nutrition support. Caution should be taken when using such feeding protocols and patients encouraged to consider specialised tube feeds which contain food derived ingredients such as Compleat Paediatric.

Local guidance should be followed regarding provision of blended diet tube feeding regimens in hospital and patients should be referred to the community dietitian.

Where locally agreed blended diet guidance is not available, consult the British Dietetic Association Blended diet toolkit for further advice and risk assessment. https://www.bda.uk.com/resource/the-use-of-blended-diet-with-enteral-feeding-tubes.html

Immunocompromised patients will need full risk assessment before embarking on the use of a blended diet and the PTC consultant and dietitian informed of any patient who is following such a diet.

Parenteral Nutrition (PN)
PN should only be used when the gut is not functioning. It is not an emergency procedure. Centres should follow local policies and procedures regarding PN usage.
Indications for PN

- Severe mucositis
- Severe vomiting (on anti-emetics) and/or Diarrhoea
- Ileus, and if the duration of being NBM estimated to be for an extended period, i.e. > 5 days

- Typhlitis
- Failure to establish adequate enteral nutrition within 3-5 days

Contraindications:

- Functioning Gut
- Likely to need PN for less than 5 days (benefit/burden of PN should be considered)
- No CV access

The pharmacist and dietitian, in collaboration with the multidisciplinary tea, should assess parenteral nutrition requirements. If possible, trophic feeds should be maintained (small volume of enteral tube feeding e.g. 5mls an hour) to help maintain gut wall integrity and reduce the chance of bacterial translocation.

Dental health

Good oral hygiene is vital in our patient group. This is even more so when they are prescribed nutritional supplement drinks, which are not only rich in proteins, fats, vitamins and minerals, but will also contain large amounts of sugar to provide adequate calories for development and growth. Children should be encouraged to brush their teeth twice a day throughout treatment and beyond. Taste and sensory changes may necessitate experimenting with different types and flavours toothpastes and in cases of mucositis a softer toothbrush or foam stick may be required.

Alternative /Complimentary diets and Supplements

Vitamin and Mineral Supplements

These are not routinely prescribed and are not usually needed by patients receiving enteral tube feeding. Whilst such supplements may be desirable for those on a restrictive diet, palatability and size of tablet often limit their use. Most of the widely available 'chewable' supplements contain a very limited number of vitamins. Before embarking on a course of vitamin/mineral supplements or herbal supplements, parents should contact the hospital pharmacy drug information service to check for potential drug-nutrient interactions. Vitamin D supplementation should be continued in children under 5 years and levels checked in patients who have had long inpatient stays or have taken steroids over a prolonged period. Fish oil supplements are not routinely encouraged due to possible drug interactions and potential impact on platelet function.

There is an increasing trend to follow diets purporting to cure or support cancer treatment. There is no evidence to support such diets and they tend to be very restrictive, time-consuming, and expensive to follow. If a parent /carer or patient wish to follow such a diet or are following such a diet, please refer to the dietitian at the PTC for a full nutrition evaluation. The dietitian will aim to work with the family and ensure the diet is nutritionally balanced. Most of these diet regimens also include the use of high doses of vitamin and minerals and herbal products that may potentially interact with other medication.

Healthy, balanced eating

A large number of children undergoing treatment for cancer (especially haematological cancers particularly ALL and lymphoma and some CNS tumours) may struggle with weight gain during their treatment in part due to use of steroids.

For patients that are unlikely to suffer from weight loss and under nutrition nutritional advice should focus on the promotion of an appropriate weight for height and general principles of healthy eating and a balanced diet. Such patients are unlikely to need food fortification advice, additional high energy/protein snacks and do not need complex meals in the middle of the night. Children should be encouraged to eat a mixed diet and fruit and vegetable intake should be promoted throughout treatment and beyond. Early

instigation of such advice is recommended. Weight, height and BMI should be monitored, and advice adjusted as necessary.

Families can be encouraged to use reputable resources such has the NHS website 'live well section, https://www.nhs.uk/healthier-families (formally 'Change for Life') and to useful resources such as the infant and Toddler Forum https://infantandtoddlerforum.org/ and the Caroline Walker Trust https://www.cwt.org.uk/

Advice on exercise during treatment can be found in the CCLG Patient information booklet **'Keeping your child active during and after treatment'**(available from the CCLG and online)

Excessive weight gain and poor eating habits

Some patients, particularly those undergoing treatment composing of regular steroid use, may experience excess weight gain and erratic eating patterns. Early referral to the local dietitian for weight maintenance advice and regular monitoring is advisable. Parents may also need guidance on the importance of maintaining regular food patterns and in avoiding an overdependence on high calorie 'snack' foods and confectionary, both during and after treatment. The infant and Toddler forum has useful resources regarding dealing with fussy eating.

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3. Nutritional Requirements for children in Health and Disease. The Dietetic Dept - Great Ormond Street, September 2000 - Third Edition.
4. Contact for 'Helping your child to eat' booklet, CCLG tel:01162494460, email:info@cclg.org.uk website www.cclg.org.uk
5. Food Standard's Agency alert re Listeria associated with smoked fish and vulnerable patients https://www.food.gov.uk/news-alerts/news/vulnerable-consumers-advised-of-ongoing-risk-of-listeria-associated-with-ready-to-eat-smoked-fish (accessed 10.10.22)
6. NHS Food Safety Advice: including https://www.nhs.uk/conditions/baby/weaning-and-feeding/foods-to-avoid-giving-babies-and-young-children, https://www.cuh.nhs.uk/patient-information/food-safety-advice-for-people-who-are-at-an-increased-risk-of-infection/

General Resource:

Shaw,V (Ed) (2020) Clinical Paediatric Dietetics (5th Ed), Wiley, Oxford. Especially useful Chapter18 : Childhood cancers and Immunodeficiency pp371

10.

MOUTH CARE PROTOCOL AND MUCOSITIS

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10. Mouth Care Protocol and Oral Mucositis

Introduction

Oral health refers to the condition of the mouth and teeth, which enables children and young people to perform the important functions of eating, drinking, speech and breathing. Maintaining good oral health also has links to the psychosocial elements of body confidence and socialising (Militi, et al., 2021).

Oral hygiene is an integral part of health care. It encompasses health promotion, preventative strategies, assessment and treatment interventions. Assessment and delivery of appropriate oral care can prevent potential infections as well as reduce distress and discomfort (Myatt, 2021). Infections in the mouth can spread and lead to complications such as sepsis (American Academy of Pediatric Dentistry, 2013). A reduced oral intake due to discomfort will compromise the patient's ability to meet their nutritional needs and may necessitate the use of parenteral nutrition prolonging hospital stay (Miller, et al. 2012).

The principal objective of oral care is to maintain the mouth in good condition. It specifically aims to:

- Keep the oral mucosa clean, soft, moist and intact.
- Keep the lips clean, soft, moist and intact.
- Remove food debris / dental plaque without damaging the gums.
- Alleviate pain / discomfort in the mouth.
- Prevent halitosis and freshen the mouth.
- Decrease the risk of oral and systemic infection.
- Increase general well-being.

A common side effect of cytotoxic agents is mucositis, a painful inflammation and ulceration of the mucous membrane that can affect the entire gastrointestinal tract from the mouth to the anus. Mucositis specifically develops in response to receiving cytotoxic therapy or radiation (Bennett, 2016) and should therefore be considered distinct from stomatitis, which refers to any inflammatory reaction affecting the oral mucosa (Pulito et al., 2020).

Symptoms of oral mucositis initially present as mucosal erythema, which is accompanied by an altered sense of taste. For some patients, symptoms will not develop further than this. However, they could experience more severe mucosal changes, typically ulcerative lesions. Mucositis ulcers tend to be deeper and markedly more painful than other types of ulcers. They tend to appear in the fleshy movable areas of the mucosa, including the cheeks, floor of the mouth, tongue and soft palate (Elad et al., 2022). The World Health Organisation (WHO) (1979) developed a grading system for oral mucositis based on clinical appearance and perceived discomfort level, with grades 1 and 2 being relatively mild and grades 3 and 4 being severe.

Grade	Description
Mild	
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
Severe	
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

WHO (1979) Oral Mucositis Grading Scale

To enable appropriate mouth care to be implemented, an oral assessment is required. It is a vital step in the planning of effective mucositis management. A thorough assessment should cover the eight aspects of the mouth: swallow, lips and corner of the mouth, tongue, saliva, mucous membranes, gingiva, teeth and voice. Regular and thorough mouth care is essential in all children undergoing cancer therapy, even if they are not eating. Certain conditions and treatments are directly correlated with a greater mucositis risk which will determine the level of intervention needed for the child/young person (Miller, 2012). Evidence-based guidelines around mouth cares have been developed for national use and are available at www.cclg.org.uk.

Oral and Dental Assessment

Assessing the oral cavity involves a thorough and systematic approach. This is essential so that any changes are monitored, and appropriate treatment implemented.

At Diagnosis:

- Ideally oral and dental assessment at diagnoses should be by a dentist linked to the Principal Treatment Centre.
- Any treatment required should be undertaken by a consultant or specialist paediatric dentist.

During Oncology Treatment:

- An oral assessment should be completed as part of each admission process and at least daily thereafter.
- Use of an oral assessment instrument such as the OAG is recommended (Gibson et al., 2010). The assessment procedure should be explained to the child/young person and family, including why the assessment is necessary and what it entails. Conditions that compromise oral well-being should also be considered when undertaking an oral assessment.
- Wherever possible the child/young person should be involved in the assessment. When assessing the mouth of a young child it is advisable to have a second adult present to support the child's head. A good source of light will also be required to examine the oral cavity fully.
- It is the responsibility of the nurse managing the child/young person's care to assess the oral mucosa and decide on subsequent methods of oral hygiene in discussion with the medical team. Mouth cares should occur twice daily as a minimum (Department of Health (DH), 2017) and frequency increased as the condition of the child/young person's mouth dictates.
- All assessments and interventions need to be documented.

Post Treatment:

- By usual dental provider with clear communication and guidance from the Principal Treatment Centre.

Mechanical Cleaning:

Toothbrushes:
A small headed, soft, nylon bristled toothbrush, with round ended filaments should be used to brush/clean teeth. These should be changed every three months or sooner if the bristles become splayed (DH, 2014).

Considerations while the child/young person is receiving treatment: the toothbrush should be for their sole use only. It should be changed regularly, some suggest replacement after each neutropenic phase (Qutob et al., 2013). Air-drying the toothbrush between uses is also recommended.

There are many forms of powered toothbrush available (electric, sonic, ultrasound) which have differing modes of action – (side to side, rotation oscillation, circular and more). Brushes that work with a rotation oscillation action remove more plaque and reduce gingivitis more effectively than a manual toothbrush, and may be more effective than other modes of action (Yaacob et al, 2014). However, the most important factor is that whether manual or powered the brushes are used effectively twice a day (DH, 2014). As the bristles are hard, they are not advisable for children with a fragile mucosa.

Foam Cleaning Sponges

Cleansing sponges alone are ineffective at removing plaque (Johnstone, Spence and Kozioi-McLain, 2010). However, they can be used as a temporary measure, or combined with a toothbrush to remove debris and cleanse the mouth when a child is unable to brush their teeth effectively.

Foam cleaning sponges are useful in the following situations:

- When a child has no teeth – moisten sponges with water (UKCCSG-PONF, Mouth care group 2006).
- When a child or young person has severe mucositis and it becomes too painful to brush (UKCCSG-PONF Mouth care group, 2006).
- For palliative care situations when comfort is the only intended outcome (Sargeant and Chamley, 2013).

Staff should be aware of the Medicines and Healthcare products Regulatory Agency (MHRA) (2012) medical device alert that foam heads of oral swabs may detach from the stick during use and present a choking hazard for patients. Instructions for use by the manufacturer should be followed for safety.

Dental Floss

Along with toothbrushing, dental floss has been found to be an effective method of removing plaque as it reaches harder interproximal spaces to dislodge food particles. Dental floss must be used according to manufacturer's safety guidance and is not recommended for children under 10 years of age depending on the system and technique used (Lin et al., 2020).

Cleansing Agents:

Fluoride Toothpaste

For the maximum prevention of tooth decay for children and young adults use toothpastes containing 1350-1500 parts per million (ppm) fluoride (DH, 2017) which strengthens tooth enamel and decreases the risk of dental cavities (Walsh et al., 2019).

Chlorhexidine mouthwash

Chlorhexidine gluconate has antimicrobial and antiplaque properties and is shown to be well tolerated by patients over the age of 6 years old receiving chemotherapy (Cheng, 2004). Chlorhexidine does not have any hazardous adverse side effects but if used for a long period, it can lead to reversible discoloration of teeth and mucous membranes. No studies definitively prove its effectiveness in the prevention or treatment of radiotherapy/chemotherapy induced mucositis (Cardona et al., 2017). Therefore, Chlorhexidine is not routinely recommended for this patient group. Unless the child or young person is

unable to brush their teeth, in which case foam sponges moistened with chlorhexidine may be used in the treatment of gingivitis and plaque control, two common oral diseases in these patients because of their poor oral hygiene (McGuire et al., 2013).

Polyvinylpyrrolidone-Sodium Hyaluronate Gel (Gelclair®)

Gelclair® has been shown to reduce the pain associated with oral mucositis and inhibit unwanted bacteria colonisation in the mouth (Vorkurka et al., 2011).

Gelclair® is technically classified as a medical device (specifically category 2a) rather than a licensed medicine and appears in the Drug Tarrif Part IXA appliances as an oral film forming agent. Whilst the company does not provide specific information around its use in children, Great Ormond Street Hospital and the Royal Marsden Hospital have a wealth of experience using it with paediatric cancer and bone marrow transplant patients.

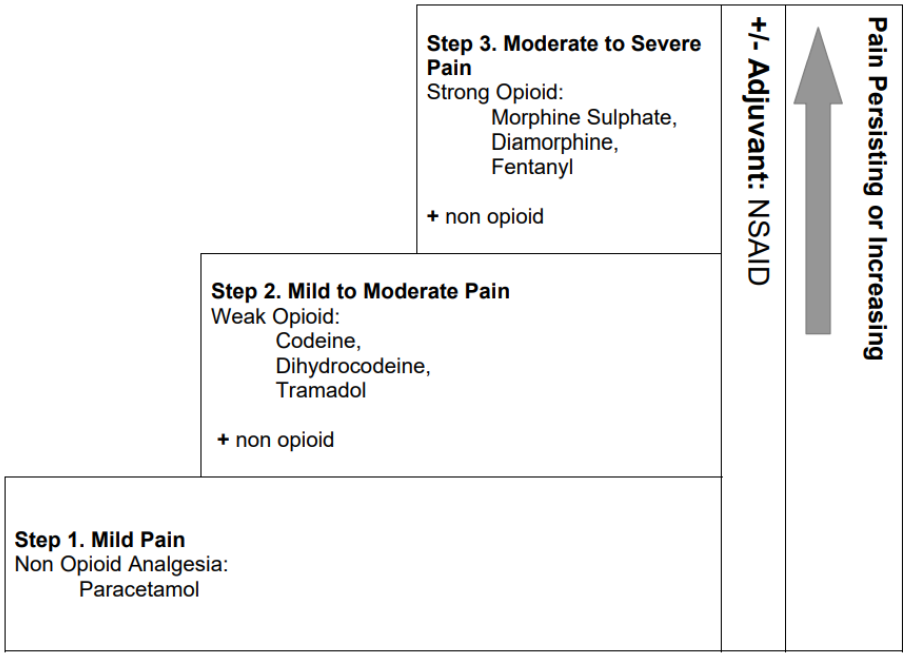
Some pharmacy departments are having trouble obtaining Gelclair®, as it is not approved on the formulary. It may be possible to obtain Gelclair® locally or from an outside pharmacy.

Analgesia:

Pain relief may be necessary to relieve the discomfort of oral mucositis in children and young people with cancer. Pain associated with oral mucositis can be severe and regular pain assessments should be completed to provide a complete picture of the symptom (Gibson et al, 2006). There are several topical agents available which may reduce oral pain because they invoke an effective anti-inflammatory response, for example benzydamine which comes as a mouthwash or spray, and sucralfate suspension (Colella et al., 2023).

Although a variety of approaches to pain management are used, analgesics still form the backbone of any strategy. In most situations analgesics of gradually increasing strength are used, according to the WHO analgesic ladder (1986). However, if a child or young presents in severe pain, then the first steps of the ladder may need to be by-passed. It is essential that analgesics on all steps are given regularly, and that compliance is checked before moving on to the next step of the ladder. Opioid analgesia should be used over paracetamol and NSAIDs for cancer patients (UKCCSG-PONF, Mouth care group 2006).

WHO analgesic ladder (1986)



Other Supportive Therapies

The National Institute for Health and Care Excellence (NICE) has issued guidance on the use of low-level laser therapy (LLLT) for the prevention and treatment of oral mucositis (NICE, 2018). However, the supporting evidence is largely adult based and no specific protocol for its delivery has been supplied yet. LLLT is thought to work by increasing ATP synthesis in the mitochondria of cells, to enhance cell function and speedy healing (Chung et al., 2012). Whilst extensive trials have been carried out across Europe evidencing its safety for use in children and adults (Sung et al., 2015), LLLT is currently only being used within one centre in England and Wales - Sheffield Children's Hospital (Redman et al., 2019).

There is a consensus that different protocols would be needed for different groups of patients and further studies would be helpful to elicit recommended treatment times for each application of LLT, since they widely differ in all the controlled trials found (ranging from 10 - 230 seconds) (Abramoff et al., 2008; Ahmed et al., 2015; Amadori et al., 2016; Cruz et al., 2007; de Castro et al., 2013; Kuhn et al., 2009; Soto et al., 2015; and Vitale et al., 2017). No studies have reported on how expensive or easy it is to set up this treatment modality and not every centre will have the infrastructure or funding to support it without considerable planning.

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11.

HYPERTENSION

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11. Hypertension

Hypertension and nephrotoxicity are recognised complications in paediatric cancer care. Severe or long-standing hypertension carries a high risk of morbidity and mortality, if left untreated. The aetiology of hypertension in children with cancer is multi-factorial. The most common cause of hypertension is pain or anxiety related and is typically associated with tachycardia. However, hypertension can also be secondary to the underlying oncological diagnosis (Wilm's tumour, Neuroblastoma, hypertension in the context of raised intra-cranial pressure for brain tumours), side effects of the treatment (Steroids, Calcineurin inhibitors, Fluid overload) or occasionally related to the underlying cancer association/pre-disposition syndromes (Neurofibromatosis, Von Hippel Lindau Syndrome).

Borderline hypertension/ Asymptomatic "standard' hypertension can be managed with a "wait and watch" approach over 1-2 days before treatment is initiated, whereas, marked hypertension (> 95th centile) may need to be managed urgently in view of the risk of hypertensive encephalopathy. The risk of acute hypertensive complications is aggravated in patients who have other co-morbidities/organ dysfunction. Medical management of hypertension can be complicated, and the choice of therapy depends on the severity of the hypertension and the underlying cause. This needs close liaison with the Primary Treatment Center (PTC) multi-disciplinary teams.

Measurement of Blood Pressure in Children:

The first important issue is to confirm is the patient has true high blood pressure (BP). Correct measurement of BP on children requires the use of a cuff that is appropriate to the size of the child's upper right arm. BP measurements are over-estimated to a greater degree with a cuff that is too small than they are under-estimated by a cuff that is too large. Measurements should typically be taken while the child is resting comfortably in the sitting position for at least 5 minutes. The inflatable cuff should cover 80% of the arm circumference and 40% of the arm length. Oscillometric measurements are widely used in the clinical setting but are known to overestimate the patient's BP. Due to this, elevated BP readings (>90th centile) obtained by oscillometric machines should be confirmed by an auscultatory BP measurement in children > 5 years or by using a Doppler in children < 5 years of age. It is important to note that serial blood pressure measurements are required to get an accurate picture (especially in the infant age group) paying close attention to the state of the child when the readings are being taken (and documented as such). In some circumstances, it can be difficult to define the presence of high blood pressure and discussion with the PTC renal team is advised. Ambulatory BP monitoring may be offered and has been used as a useful adjunct in establishing the diagnosis. Blood pressure readings consistently above the 95th centile for age, sex and height should normally be treated.

Current Definition of Hypertension:

In 2017, the American Academy of Pediatrics (AAP) published an updated Clinical Practice Guideline (CPG) for the screening and management of high blood pressure in children and adolescents. This guideline had not been updated since 2004, with the most clinically relevant revision to include new normative paediatric blood pressure tables based on normal weight children (excluding overweight and obese children) and including a simplified blood pressure (BP) classification for adolescents ≥13 years of age that aligns with adult BP guidelines. Other changes include replacement of the term "pre-hypertension" with "elevated blood pressure" for values that are ≥90th percentile but <95th percentile for age and height. For children, thresholds for the definitions of elevated blood pressure and hypertension according to age and height remain the same: blood pressure ≥90th and <95th percentile designates elevated blood pressure and ≥95th percentile indicates hypertension. For adolescents ≥13 years of age, the criteria for high blood pressure now align with the updated adult guideline that defines measurements ≥120/80 as elevated

blood pressure and ≥130/80 as meeting criteria for hypertension. Appropriate centile charts for BP in infants, boys and girls are enclose in Appendices 2-4.

Comparison of Definitions of the Updated 2017 American Academy of Pediatrics Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents versus the 2004 Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents

	2017 AAP CPG		2004 Fourth Report
	<13 Years	≥13 Years	
Normal BP	<90th percentile	<120/<80	<90th percentile
Elevated BP*	≥90th to <95th percentile or 120–129/< 80	120–129/<80	≥90th to <95th percentile or >120/80
Stage 1 HTN	≥95th to <95th percentile + 12 mmHg or 130/80 to 139/89	130–139/80-89	≥95th to <99th percentile + 5 mmHg
Stage 2 HTN	≥95th percentile + 12 mmHg or ≥140/90	≥140/90	≥99th percentile + 5 mmHg

Management of Hypertension:

In a new presentation, the duration of hypertension may not be known so care must be taken to lower the blood pressure. The decision to initiate pharmacological treatment will depend on the presence of symptoms, level of BP elevation, presence of end organ damage or any other cardiovascular risk factors. The choice of therapy will be guided by the likely underlying cause and further discussion with PTC/Paediatric nephrology team is advised prior to starting treatment.

'Standard' Hypertension:

Children with severe hypertension at presentation may have extracellular fluid depletion, the administration of diuretics at this point is contra-indicated. Unless signs of fluid overload are obvious, it is safer to reserve diuretics until the hypertensive state is stabilised. Tumour associated or therapy related hypertension should be treated in the same way.

1) First line:
   Calcium channel blockers (such as Nifedipine and Amlodipine) are quite safe and well tolerated. Nifedipine is generally used as a first line agent. It is recommended to use the modified release preparation to help reduce the blood pressure gradually. Nifedipine liquid preparation/drops are not recommended as the drop in BP can be unpredictable. If the patient continues to be hypertensive, Amlodipine can be started for maintenance therapy.

2) Second line:
   Angiotensin Converting Enzyme inhibitors and Angiotensin Receptor Blockers are good 2nd line agents, but caution should be exercised in patients with renal impairment, tumours affecting both kidneys/compressing bilateral renal vasculature. They should only be prescribed after discussion with paediatric nephrology team.

3) Additional agents such as beta-blockers (given cardiac function is acceptable on Echocardiogram or no history of asthma) and Hydralazine or Doxazosin (if an IV preparation is required) can also be considered if deemed appropriate by the paediatric nephrology team.

'Catecholamine Excess' Hypertension:

Paragangliomas/Pheochoromocytomas may be associated with hypertension due to the secretion of excess catecholamines and should be managed under close guidance by the PTC multidisciplinary teams. Communication between the teams is vital and should be established at the earliest opportunity to allow adequate time for planning. A target BP reduction should be discussed with the PTC (<50th centile for age and height). Alpha blockade therapy (Phenoxybenzamine/Doxazosin) should be started as soon as a diagnosis has been made. It often takes 2 weeks to a month before the child is adequately blocked to be safe for an anaesthetic. Beta blockade with Propranolol is then instituted following alpha blockade to off-set reflex tachycardia. Standard paediatric dosing can be started at least a week prior to the surgery and should never be given prior to alpha blockade as this can lead to hypertensive crisis. Calcium channel blockers can also be used in these cases.

Hypertensive Crisis / Acute Hypertensive Encephalopathy:

This is an Emergency and should be managed in an HDU/PICU!
Discuss with the PTC urgently!

This is defined as a severe elevation of the blood pressure associated with a clinical picture of rapid and progressive CNS, visual, myocardial, haematological or renal deterioration. Emergency intervention is needed to protect vital organs under close guidance of the PTC and the nephrology team until the patient is safely retrieved/transferred. The **goal** of the therapy is to reduce the BP by **1/3rd in the first 12 hours** followed by another **1/3rd reduction the next 24 hours**. A target BP must be clearly defined at the start of treatment.

It is necessary to use drugs with a rapid action, but these require careful administration to prevent sudden hypotension and resulting failure of auto regulation mechanisms. Drugs which can be infused intravenously to finely control BP during the critical early phase of management are preferred. Labetalol and sodium nitroprusside are both effective. Hydralazine may be used in milder cases particularly if high dependency care is not available. When commencing an IV drug, always have a saline infusion set-up and connected, to enable immediate saline bolus if the BP drops too quickly. All patients should have frequent observations for neurological status and should be treated in a high dependency unit.

Oral/sublingual hypotensive agents or diuretics are contraindicated in the initial management of hypertensive crisis. These are best reserved until the blood pressure is safely controlled. If the child is having a convulsion a suitable anticonvulsant should be administered intravenously in addition to steps being taken to reduce blood pressure.

Important!

Repeated checks on visual acuity and pupillary reactions to light are essential because the risk of optic nerve infarction in children with accelerated hypertension is considerable. The loss of vision or pupillary reaction to light as the BP is reduced is an **emergency** that justifies raising the BP by intravenous saline or plasma. Dexamethasone maybe required.

Posterior Reversible Encephalopathy Syndrome (PRES):

The features of this syndrome may develop as a part of a hypertensive crisis and are characterised by sudden onset of:

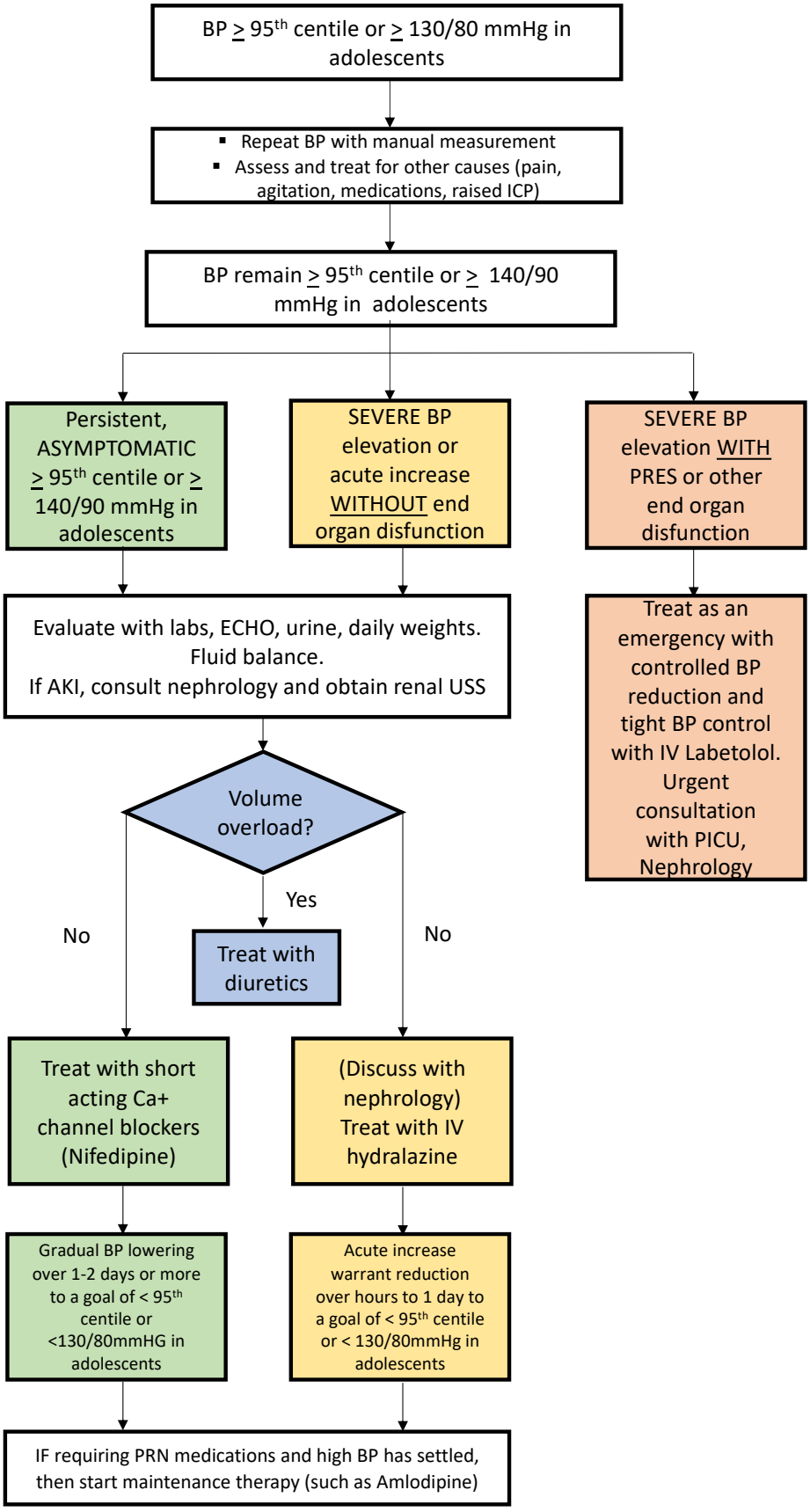
- Seizure
- Reduce level of consciousness
- Cortical blindness
- MRI changes (particularly affecting the occipital lobes)

This can be seen in an oncology patient with tumour lysis syndrome, receiving chemotherapy or in a post-stem cell transplant patient. Symptoms and signs often reverse as rapidly as they appear and prognosis is generally good with prompt control of blood pressure, withdrawal of agents which precipitated the hypertension and correction of hypomagnesaemia.

Drugs used in the treatment of hypertension (refer to BNFc for doses)

Drug	Comments
Amlodipine	If necessary, increase at intervals of 1-2 weeks
Atenolol	Should be used only after discussion with Paediatric renal team.
Captopril	Should be used only after discussion with Paediatric renal team. Monitor blood pressure carefully for 1-2 hours after initial dose
Lisinopril	Should be used only after discussion with Paediatric renal team. Monitor blood pressure carefully for 1-2 hours after initial dose
Frusemide	Can be used when there are signs of volume overload
Hydralazine	IV preparation can be used in Hypertensive crisis with careful monitoring for hypotension
Labetalol	**Should only be given in an area that can carry out all the necessary checks**
Nifedipine	**Moderate release preparations are recommended. Avoid using nifedipine liquid/drops as BP drop can be unpredictable**
Sodium Nitroprusside	**Should only be given in an area that can carry out all the necessary checks**
Spironolactone	Can be used when there are signs of volume overload with K sparing effect

Flow Chart : Summary of Hypertension Management in Paediatric Oncology Patient



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Neonates: estimated BP, after 2 weeks of age, in infants from 26-44 weeks post-conceptual age

(Derived from Dionne JM et al, Pediatric Nephrology. 2012)

Postconceptional age	50th percentile	95th percentile	99th percentile
44 Weeks			
SBP	88	105	110
DBP	50	68	73
MAP	**63**	**80**	**85**
42 Weeks			
SBP	85	98	102
DBP	50	65	70
MAP	**62**	**76**	**81**
40 Weeks			
SBP	80	95	100
DBP	50	65	70
MAP	**60**	**75**	**80**
38 Weeks			
SBP	77	92	97
DBP	50	65	70
MAP	**59**	**74**	**79**
36 Weeks			
SBP	72	87	92
DBP	50	65	70
MAP	**57**	**72**	**71**
34 Weeks			
SBP	70	85	90
DBP	40	55	60
MAP	**50**	**65**	**70**
32 Weeks			
SBP	68	83	88
DBP	40	55	60
MAP	**48**	**62**	**69**
30 Weeks			
SBP	65	80	85
DBP	40	55	60
MAP	**48**	**65**	**68**
28 Weeks			
SBP	60	75	80
DBP	38	50	54
MAP	**45**	**58**	**63**
26 Weeks			
SBP	55	72	77
DBP	30	50	56
MAP	**38**	**57**	**63**

Boys: blood pressure table (Flynn JT, Kaelber DC, Baker-Smith CM, et al. *Pediatrics.* 2017)

TABLE 4 BP Levels for Boys by Age and Height Percentile

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th + 12 mm Hg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th + 12 mm Hg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (in)	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th + 12 mm Hg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (in)	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th + 12 mm Hg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (in)	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th + 12 mm Hg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (in)	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th + 12 mm Hg	122	122	123	124	126	127	128	83	83	84	85	85	86	86

Boys: blood pressure table (Flynn JT, Kaelber DC, Baker-Smith CM, et al. *Pediatrics.* 2017)

TABLE 4 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.8	48.6	50	51.6	53.2	54.6	55.5	47.8	48.6	50	51.6	53.2	54.6	55.5
	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th + 12 mm Hg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (in)	49.6	50.5	52	53.7	55.4	56.9	57.9	49.6	50.5	52	53.7	55.4	56.9	57.9
	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th + 12 mm Hg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height (in)	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th + 12 mm Hg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (in)	53	54	55.7	57.6	59.6	61.3	62.4	53	54	55.7	57.6	59.6	61.3	62.4
	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th + 12 mm Hg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (in)	55.2	56.3	58.1	60.1	62.2	64	65.2	55.2	56.3	58.1	60.1	62.2	64	65.2
	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th + 12 mm Hg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13	Height (in)	57.9	59.1	61	63.1	65.2	67.1	68.3	57.9	59.1	61	63.1	65.2	67.1	68.3
	Height (cm)	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	95th + 12 mm Hg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14	Height (in)	60.6	61.8	63.8	65.9	68.0	69.8	70.9	60.6	61.8	63.8	65.9	68.0	69.8	70.9
	Height (cm)	153.8	156.9	162	167.5	172.7	177.4	180.1	153.8	156.9	162	167.5	172.7	177.4	180.1
	50th	105	106	109	111	112	113	113	60	60	62	64	65	66	67
	90th	119	120	123	126	127	128	129	74	74	75	77	78	79	80
	95th	123	125	127	130	132	133	134	77	78	79	81	82	83	84
	95th + 12 mm Hg	135	137	139	142	144	145	146	89	90	91	93	94	95	96

Boys: blood pressure table (Flynn JT, Kaelber DC, Baker-Smith CM, et al. *Pediatrics.* 2017)

TABLE 4 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	62.6	63.8	65.7	67.8	69.8	71.5	72.5	62.6	63.8	65.7	67.8	69.8	71.5	72.5
	Height (cm)	159	162	166.9	172.2	177.2	181.6	184.2	159	162	166.9	172.2	177.2	181.6	184.2
	50th	108	110	112	113	114	114	114	61	62	64	65	66	67	68
	90th	123	124	126	128	129	130	130	75	76	78	79	80	81	81
	95th	127	129	131	132	134	135	135	78	79	81	83	84	85	85
	95th + 12 mm Hg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16	Height (in)	63.8	64.9	66.8	68.8	70.7	72.4	73.4	63.8	64.9	66.8	68.8	70.7	72.4	73.4
	Height (cm)	162.1	165	169.6	174.6	179.5	183.8	186.4	162.1	165	169.6	174.6	179.5	183.8	186.4
	50th	111	112	114	115	115	116	116	63	64	66	67	68	69	69
	90th	126	127	128	129	131	131	132	77	78	79	80	81	82	82
	95th	130	131	133	134	135	136	137	80	81	83	84	85	86	86
	95th + 12 mm Hg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17	Height (in)	64.5	65.5	67.3	69.2	71.1	72.8	73.8	64.5	65.5	67.3	69.2	71.1	72.8	73.8
	Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
	50th	114	115	116	117	117	118	118	65	66	67	68	69	70	70
	90th	128	129	130	131	132	133	134	78	79	80	81	82	82	83
	95th	132	133	134	135	137	138	138	81	82	84	85	86	86	87
	95th + 12 mm Hg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[77]

Girls: blood pressure table (Flynn JT, Kaelber DC, Baker-Smith CM, et al. *Pediatrics.* 2017)

TABLE 5 BP Levels for Girls by Age and Height Percentile

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	29.7	30.2	30.9	31.8	32.7	33.4	33.9	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	90th	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	95th	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	95th + 12 mm Hg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height (in)	33.4	34	34.9	35.9	36.9	37.8	38.4	33.4	34	34.9	35.9	36.9	37.8	38.4
	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	50th	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	90th	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th + 12 mm Hg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (in)	35.8	36.4	37.3	38.4	39.6	40.6	41.2	35.8	36.4	37.3	38.4	39.6	40.6	41.2
	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	50th	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	90th	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th + 12 mm Hg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (in)	38.3	38.9	39.9	41.1	42.4	43.5	44.2	38.3	38.9	39.9	41.1	42.4	43.5	44.2
	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	50th	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	90th	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (in)	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57
	90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th + 12 mm Hg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (in)	43.3	44	45.2	46.6	48.1	49.4	50.3	43.3	44	45.2	46.6	48.1	49.4	50.3
	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	50th	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	90th	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th + 12 mm Hg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (in)	45.6	46.4	47.7	49.2	50.7	52.1	53	45.6	46.4	47.7	49.2	50.7	52.1	53
	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	50th	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	90th	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th + 12 mm Hg	121	122	123	124	125	126	127	84	84	85	85	86	86	87

Girls: blood pressure table (Flynn JT, Kaelber DC, Baker-Smith CM, et al. *Pediatrics.* 2017)

TABLE 5 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.6	48.4	49.8	51.4	53	54.5	55.5	47.6	48.4	49.8	51.4	53	54.5	55.5
	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	50th	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	90th	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th + 12 mm Hg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (in)	49.3	50.2	51.7	53.4	55.1	56.7	57.7	49.3	50.2	51.7	53.4	55.1	56.7	57.7
	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	50th	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	90th	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th + 12 mm Hg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height (in)	51.1	52	53.7	55.5	57.4	59.1	60.2	51.1	52	53.7	55.5	57.4	59.1	60.2
	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	50th	96	97	98	99	101	102	103	58	59	59	60	61	61	62
	90th	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th + 12 mm Hg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (in)	53.4	54.5	56.2	58.2	60.2	61.9	63	53.4	54.5	56.2	58.2	60.2	61.9	63
	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	50th	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	90th	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th + 12 mm Hg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (in)	56.2	57.3	59	60.9	62.8	64.5	65.5	56.2	57.3	59	60.9	62.8	64.5	65.5
	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	50th	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	90th	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th + 12 mm Hg	130	131	132	134	136	137	138	90	90	90	90	91	91	91
13	Height (in)	58.3	59.3	60.9	62.7	64.5	66.1	67	58.3	59.3	60.9	62.7	64.5	66.1	67
	Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	50th	104	105	106	107	108	108	109	62	62	63	64	65	65	66
	90th	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	95th	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	95th + 12 mm Hg	133	134	135	136	138	138	139	91	91	91	91	92	92	93
14	Height (in)	59.3	60.2	61.8	63.5	65.2	66.8	67.7	59.3	60.2	61.8	63.5	65.2	66.8	67.7
	Height (cm)	150.6	153	156.9	161.3	165.7	169.7	172.1	150.6	153	156.9	161.3	165.7	169.7	172.1
	50th	105	106	107	108	109	109	109	63	63	64	65	66	66	66
	90th	118	118	120	122	123	123	123	76	76	76	76	77	77	77
	95th	123	123	124	125	126	127	127	80	80	80	80	81	81	82
	95th + 12 mm Hg	135	135	136	137	138	139	139	92	92	92	92	93	93	94

Girls: blood pressure table (Flynn JT, Kaelber DC, Baker-Smith CM, et al. *Pediatrics.* 2017)

TABLE 5 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	59.7	60.6	62.2	63.9	65.6	67.2	68.1	59.7	60.6	62.2	63.9	65.6	67.2	68.1
	Height (cm)	151.7	154	157.9	162.3	166.7	170.6	173	151.7	154	157.9	162.3	166.7	170.6	173
	50th	105	106	107	108	109	109	109	64	64	64	65	66	67	67
	90th	118	119	121	122	123	123	124	76	76	76	77	77	78	78
	95th	124	124	125	126	127	127	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	136	136	137	138	139	139	140	92	92	92	93	94	94	94
16	Height (in)	59.9	60.8	62.4	64.1	65.8	67.3	68.3	59.9	60.8	62.4	64.1	65.8	67.3	68.3
	Height (cm)	152.1	154.5	158.4	162.8	167.1	171.1	173.4	152.1	154.5	158.4	162.8	167.1	171.1	173.4
	50th	106	107	108	109	109	110	110	64	64	65	66	66	67	67
	90th	119	120	122	123	124	124	124	76	76	76	77	78	78	78
	95th	124	125	125	127	127	128	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	136	137	137	139	139	140	140	92	92	92	93	94	94	94
17	Height (in)	60.0	60.9	62.5	64.2	65.9	67.4	68.4	60.0	60.9	62.5	64.2	65.9	67.4	68.4
	Height (cm)	152.4	154.7	158.7	163.0	167.4	171.3	173.7	152.4	154.7	158.7	163.0	167.4	171.3	173.7
	50th	107	108	109	110	110	110	111	64	64	65	66	66	66	67
	90th	120	121	123	124	124	125	125	76	76	77	77	78	78	78
	95th	125	125	126	127	128	128	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	137	137	138	139	140	140	140	92	92	92	93	94	94	94

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[77]

12.

BASIC PRINCIPLES OF SYMPTOM MANAGEMENT

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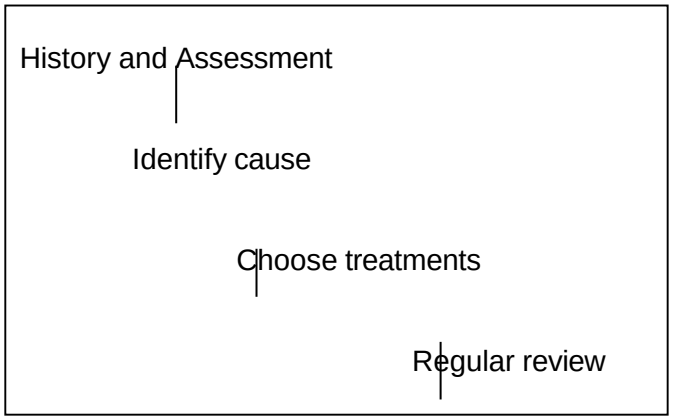
12. Basic Principles of Symptom Management

12.1 Introduction

Symptom management embraces the management of acute symptoms throughout the acute phase of active treatment, and then extends into the palliative/non-curative supportive care. It is essential, as research has shown, that the suffering experienced from treatment and its side effects will be what families remember. For those children and young people who unfortunately cannot be cured, palliative care, including rigorous attention to symptom management, will help to provide as good a quality of life as possible for the time that remains.

Each child/young person and their family respond to their symptom experience differently. The wide spectrum of cognitive ability and chronological age amongst this patient group necessitates an individualised approach to assessment and management. In addition, consideration of the best setting in which the child/young person may be assessed and managed is required. The advantages and disadvantages of each intervention must be carefully considered. The treatment must be appropriate to the symptom and the stage of illness and the chances of improving the symptom must then be balanced against the inconvenience and any discomfort caused.

It is helpful to approach the management of any symptom systematically:



When choosing pharmacological treatments in the management of symptoms for children and young people, it is important to remember that some drugs are used 'off licence' or 'off-label' and there is sometimes little data to support use in the younger age groups. Close collaboration and communication amongst health and allied healthcare professionals is essential. Advice will be available as required from the specialist palliative care team – paediatric oncology outreach nursing team, symptom control or the adult palliative care team. In addition, standard texts such as the BNFC and APPM formulary should be used.

This chapter will discuss the pharmacological management of common symptoms the child/young person may experience. However, it is very important to also consider non-pharmacological strategies for example: distraction therapy, hypnotherapy, physiotherapy and occupational therapy.

12.2 Drug doses used for Symptom / Palliative Care Management

For starting doses of drugs in symptom management, please refer to the most up to date version of BNFc/BNF. However, in symptom/palliative care management, occasionally doses may differ from BNFc/BNF, an alternative reference source is:

The Association of Paediatric Palliative Medicine Master Formulary (APPM Formulary)

[last viewed on 10/3/2023] Or refer to the most up to date version.
APPM Master Formulary

APPM Master Formulary

The Association of Paediatric Palliative Medicine Master Formulary

5th edition

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1

12.3 Nausea and vomiting

Identifying the cause of nausea and vomiting, which may be multifactorial, can help in making the logical choice of antiemetic.

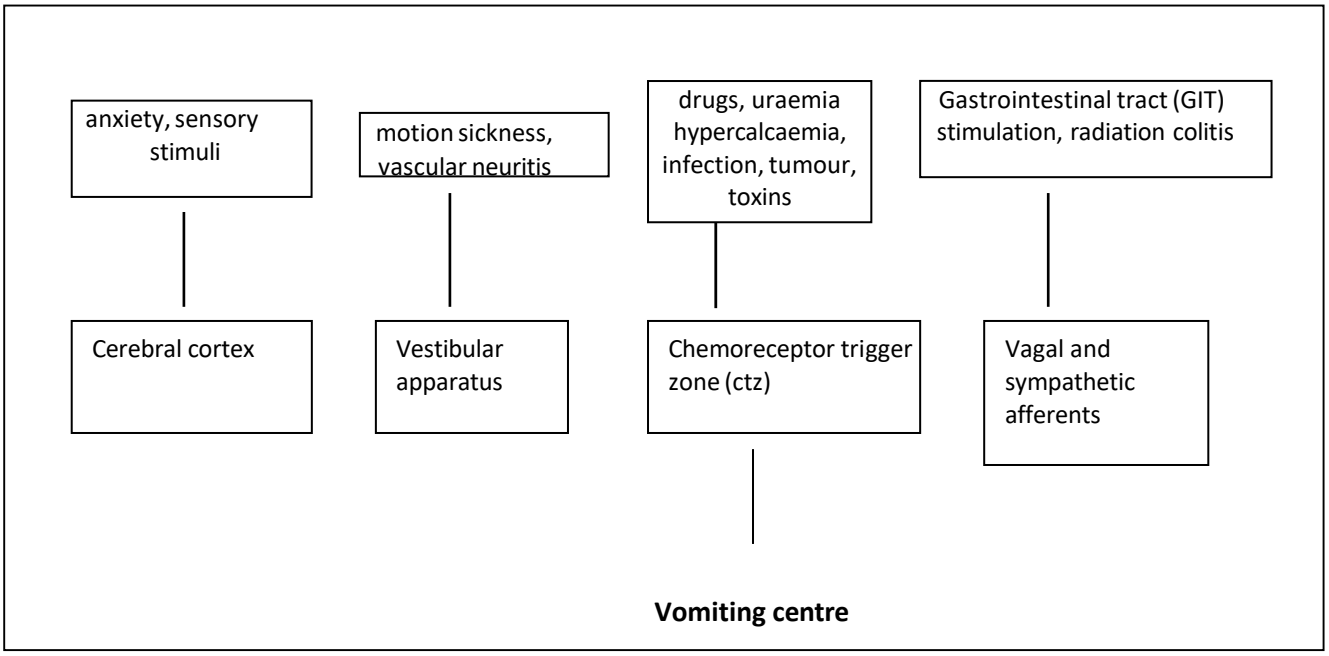
Causes of nausea and vomiting

- ***Cancer related causes***

Irritation of the upper GIT
Blood in stomach
Gastric outflow obstruction
Constipation
Abdominal mass
Anxiety
Uraemia
Cough
Pain
Raised intracranial pressure

- ***Treatment related causes***

Radiotherapy
Drug therapy e.g.
Opioids
Chemotherapy
Corticosteroids (IV)
Carbamazepine NSAIDs
Monoclonal antibodies



Antiemetics and sites of action

Anti-emetics	Site of Action
Cyclizine Hyoscine	Vomiting centre
Levomepromazine	ctz, vomiting centre
Dopamine antagonists e.g. Chlorpromazine Haloperidol Metoclopramide Domperidone Prochlorperazine	 ctz ctz, GIT ctz, GIT ctz
5 HT3 antagonists e.g. Ondansetron Granisetron	ctz, GIT
Aprepitant	Vomiting Centre

Nausea and vomiting during therapy

Managing nausea and vomiting aggressively from the start helps to gain the confidence of the child and parents and reduces the difficult problem of anticipatory vomiting. All therapy – chemotherapy, radiotherapy and surgery have the potential to trigger nausea and vomiting and as such should be assessed and treated appropriately.

The emetogenic potential of different chemotherapy agents varies (see Table 11) although susceptibility to these side effects varies from child to child. Nausea and vomiting caused by chemotherapy is generally mediated centrally via the chemoreceptor trigger zone (ctz) and peripherally via the gastrointestinal tract (GIT). Anticipatory vomiting is thought to be less common in the younger child. Anti-emetics can be given in advance of chemotherapy so that an effective blood level has been established before the chemotherapy is given and consideration should be given to anti-emetics being given at home prior to the chemotherapy. For chemotherapy with a low emetogenic potential a single anti-emetic can be given, if necessary. For those with moderate or high potential, combinations of anti-emetics will be needed. It is important to provide anti-emetics for the child to take home after chemotherapy for use until the symptoms subside (usually 2-3 days).

Nausea and vomiting in palliative care

Cyclizine and levomepromazine are commonly used for nausea and vomiting associated with raised intracranial pressure. Short pulses of dexamethasone can also be of benefit in this situation and haloperidol is a useful second line choice if cyclizine or levomepromazine are ineffective. Haloperidol and levomepromazine (should generally not be used together) may also be effective for nausea/vomiting secondary to metabolic disturbance e.g., renal failure.

Nausea and vomiting due to bowel obstruction requires specialist advice, and treatment may include steroids or chemotherapy/ radiotherapy to reduce the obstruction, as well as anti-emetics, and potentially include Octreotide (to reduce secretions) for inoperable bowel obstruction (if needed discuss with PTC before starting). (Cyclizine, levomepromazine and haloperidol are all compatible with morphine for subcutaneous/intravenous infusions).

Table 12.1 Cytotoxic agents and emetic risk

(CCLG guideline on management of chemotherapy induced nausea and vomiting. v 1.0 March 2018)

Emetogenicity of chemotherapy **Very High emetogenic potential (>90%)**	
Cisplatin Cyclophosphamide > 2g/m^2 Ifosfamide Melphalan Thiotepa *Combination chemotherapies:* Cyclophosphamide + anthracycline Cyclophosphamide + etoposide + Ifosfamide Doxorubicin + Ifosfamide Cytarabine 300 mg/m^2 + etoposide Doxorubicin + methotrexate 5g/m^2	**Step 1: Cisplatin based regimen, ifosfamide or melphalan:** **Ondansetron** IV pre chemotherapy then IV/oral regularly *and* **Dexamethasone** IV/oral (if appropriate) *and* **≥6mths: Aprepitant** oral ONCE daily for 3 days. < 6 mths:levomepromazine instead of aprepitant. **Step 1: For non- cisplatin-based regimen: Ondansetron and dexamethasone as above +/- levomepromazine (for <1yr to 17yrs)** **Step 2:** *Ensure all doses in step 1 have been optimised before moving onto step 2 and add* **Aprepitant** oral if not used in step 1 ***for subsequent cycles - >6mths old***]. Add levomepromazine for breakthrough if not given up front. See table 4 for aprepitant drug interactions and dexamethasone dose reduction. **Delayed**: give levomepromazine. Care with aprepitant and ifosfamide-see below in table 4. **Metoclopramide can be used instead of levomepromazine for > 1-year olds.**
High emetogenic potential (>90%)	
Dactinomycin Carboplatin Carmustine>250mg/m2 Cyclophosphamide 1g/m^2 - 2g/m^2 Cytarabine 3g/m^2/dose Dacarbazine Methotrexate ≥12 g/m^2	**Step 1:** **Ondansetron** IV pre chemotherapy then IV/oral regularly *and* **Dexamethasone** IV/oral (if appropriate) **Step 2:** *(Ensure all doses in step 1 have been optimised before moving onto step 2)* *Add* Levomepromazine IV/oral if not used in step 1 [add **Aprepitant** oral if not used in step 1 ***for subsequent cycles – > 6mths old***]. Refer to table 4 for aprepitant drug interactions and Dexamethasone dose reduction. **Step 3:** Consider levomepromazine infusion. [Add **Aprepitant** oral if not used in step 1 ***for subsequent cycles – for > 6mths olds).*** **Metoclopramide can be used instead of levomepromazine for > 1-year olds.** Delayed:Dexamethasone (if appropriate) iv/oral and metoclopramide (up to 5 days after chemotherapy completed)

Table 12.1 continued - Cytotoxic agents and emetic risk (CCLG guideline on management of chemotherapy induced nausea and vomiting. v 1.0 March 2018)

<table>
<tr><th colspan="4">TABLE CONTINUED: EMETOGENICITY OF CHEMOTHERAPY</th></tr>
<tr><td colspan="4">Moderate emetogenic potential (30-90%)</td></tr>
<tr><td>Aldesleukin
Arsenic trioxide
Azacitidine
Cladribine
Clofarabine
Cyclophosphamide
< 1g/m^2
Cytarabine
>200mg/m^2 to <3g/m^2</td><td>Daunorubicin liposomal
Docetaxel
Doxorubicin
Etoposide
Epirubicin
Idarubicin
Imatinib
Inotuzumab</td><td>Irinotecan
Lomustine
Methotrexate ≥1g/m^2 to <12g/m^2
Mitoxantrone
Oxaliplatin> 75mg/m2
Procarbazine
Temozolomide
Treosulfan</td><td>Step 1:
Ondansetron IV pre chemo then IV/oral regularly +/- dexamethasone. If c/I to steroids prescribe levomepromazine instead/metoclopramide.
Step 2:
Add Dexamethasone (if appropriate) mostly at step 2 than step1). Then add levomepromazine IV/oral if not already added or metoclopramide
[Consider Dexamethasone IV/oral for subsequent courses if appropriate)
<u>Delayed:</u>
Dexamethasone (if appropriate) and metoclopramide</td></tr>
<tr><td colspan="4">Low emetogenic potential (<30%)</td></tr>
<tr><td>Amsacrine ATG
Bortezomib Busulfan
Capecitabine CH14.18
Antibodies
Cyclophosphamide <300 mg/m^2
Cytarabine <200 mg/m^2
Fludarabine
5-fluorouracil
Gemcitabine</td><td>Gemtuzumab
Hydroxyurea
Intrathecals
Nilotinib Paclitaxel
Topotecan
Vinblastine/ Vincristine
Vindesine
Vinorelbine</td><td colspan="2">Step 1:
Use prn Ondansetron Step 2:
Ondansetron oral/IV regularly</td></tr>
</table>

Table 12.1 continued - Cytotoxic agents and emetic risk (CCLG guideline on management of chemotherapy induced nausea and vomiting. v 1.0 March 2018)

TABLE CONTINUED: EMETOGENICITY OF CHEMOTHERAPY **Minimal emetogenic potential (min) <10%**		
Alemtuzumab Asparaginase Bevacizumab Bleomycin Chlorambucil Dasatinib Lenalidomide Mercaptopurine	Methotrexate< 1g/m^2 Nelarabine Rituximab Sorafenib Sunitinib Temsirolimus Thalidomide Thioguanine	**Step 1** : No antiemetics required unless previous history of emesis. If previous history, use **Ondansetron**.
Anticipatory Nausea and Vomiting		
Anticipatory refers to significant nausea or vomiting prior to the delivery of chemotherapy.	**Lorazepam oral:** Give one dose evening before and one dose 1 hr before starting chemotherapy	

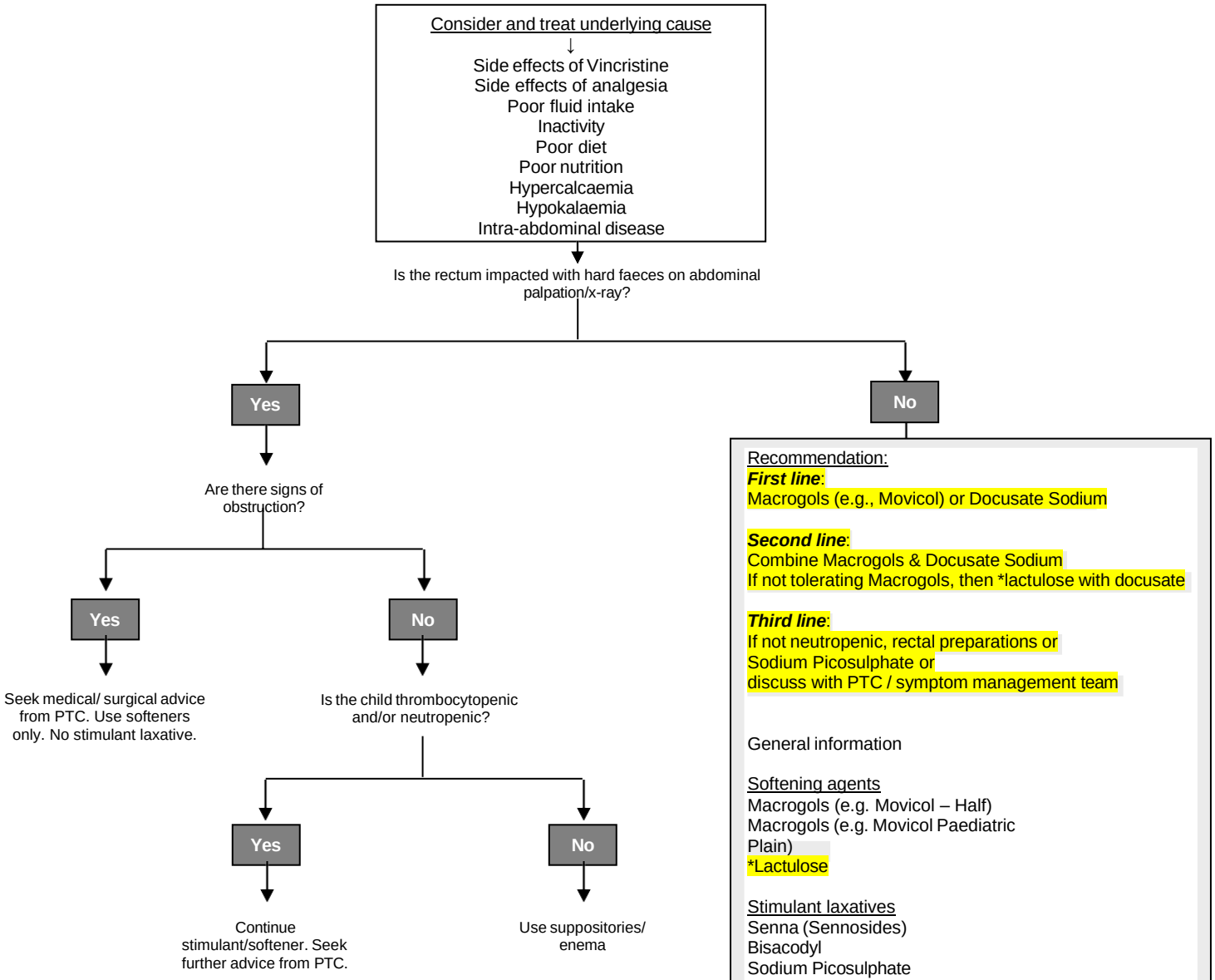
12.4 Constipation

A decrease in frequency of the passage of stools caused by either a complete or incomplete action of the bowels (Selwood et al 1999); constipation is most likely to occur as a side effect of drug treatment. Other factors such as intra-abdominal disease, poor fluid intake, inactivity, poor nutrition, cord compression, hypercalcaemia and hypokalaemia should also be considered. These underlying causes should be treated where appropriate/possible.

Prophylaxis or treatment for constipation should start with Movicol (paediatric) or sodium docusate (lactulose is less effective) If single agent proves insufficient other oral stimulants and softeners maybe required.

Doses of laxatives should be titrated up rather than always adding in a new laxative. Co-danthramer MUST only be used in children/young people with non-curative disease and should be used with caution in those who are incontinent, catheterised or in nappies as skin excoriation may occur. Occasionally rectal preparations may be needed provided the patient is not neutropenic or thrombocytopenic and all oral measures have been tried (see box). In some children where disease affects spinal cord resulting in compression, a combination approach involving oral (enteral) laxative given daily with alternate day enemas, such as sodium citrate (micralax®), should be considered to maintain regularity.

Pathway for treatment of constipation



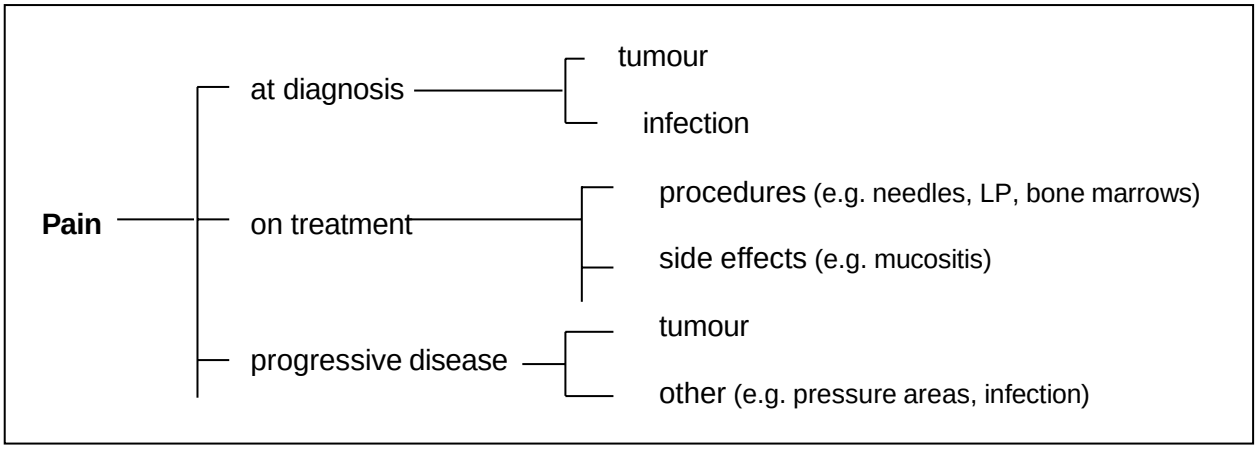
**Lactulose (MUST be used in combination with another softener, stimulant or combined softener / stimulant.*

Recommendation based on NICE guidelines with modification for haem/onc patients. ***NICE guidelines Constipation in children and young people. May 2010 last updated July 2017*** *https://www.nice.org.uk/guidance/cg99 (last read08/11/2022)*

12.5 Pain

Pain is a complex sensation related to physical, social, psychological and cultural reasons which all need to be considered in the assessment of a child/young person's pain to reflect the best choice of treatment. Problems from pain can occur throughout the disease process (see below).

Causes of pain during the disease process



12.5.1 Assessment of Pain

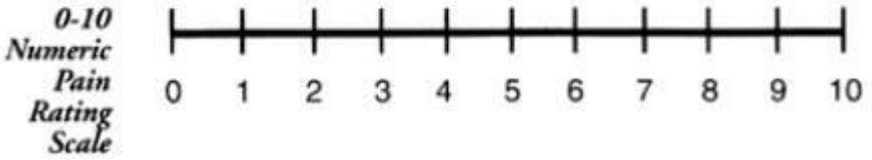
Pain is a subjective experience and the child/young person's own opinion is the best guide as to what they are feeling, but this can be limited by their level of understanding and communication skills, i.e., irritability and restlessness, reluctance to be held or unnatural stillness may be misunderstood. Parents are usually able to interpret their child's feelings but may sometimes under or over-estimate the pain experience.
Specific pain assessment tools are available, according to the child's age and ability. Body charts are helpful for all ages to locate and identify sites of pain, whilst colour scales, faces, numeric and visual analogue scales can be used to measure severity. When assessing pain, it is also important to consider psychological and cultural factors influencing the child and family and their coping skills.

Pain Tools

For those aged under 4 years of age and non-verbal children: FLACC Chart

FLACC scale	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested.	Frequent to constant quivering chin, clenched jaw.
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up.
Activity	Lying quietly, normal, position moves easily.	Squirming, shifting back and forth, tense.	Arched rigid or jerking.
Cry	No cry, (awake or asleep)	Moans or whimpers: occasional complaint.	Crying steadily, screams or sobs, frequent complaints.
Consolability	Content, relaxed	Reassured by occasional touching hugging or being talked to, distractable.	Difficulty to console or comfort.

For 4 years of age and above: Baker-Wong Faces chart or Numerical pain scale



12.5.2 Definitions of pain

Procedure-related pain

Some of the tests or procedures that children have during their treatment may be uncomfortable or painful. The need for appropriate analgesia should be anticipated. Some examples are central line insertions, bone marrow tests or lumbar punctures.
The duration of pain/discomfort experienced may be variable from a few hours to a few days and should be managed with a stepwise approach.

Persisting Pain

The WHO persisting pain guidance 2012, defines children with cancer related pain (either from treatment or tumour related causes) as having persisting pain.
Persisting pain is therefore considered to be any pain that is not related to a procedure or investigation.

The current WHO guidelines (2012) no longer recommend the use of codeine as a weak opioid for the management of persisting pain. It advocates a two-step approach from simple analgesia e.g. Paracetamol followed by the use of low doses of strong opioids e.g. morphine.

Correct use of analgesic medicines will relieve pain in most children with persisting pain due to medical illness and relies on the following key concepts:

- using a two-step strategy
- dosing at regular intervals
- using the appropriate route of administration
- adapting treatment to the individual child

Neuropathic pain

Neuropathic pain is caused by structural damage and nerve cell dysfunction in the peripheral or central nervous system (CNS). Any process that causes damage to the nerves, such as metabolic, traumatic, infectious, ischaemic, toxic, or immune-mediated pathological conditions, can

result in neuropathic pain. In addition, nerve compression or the abnormal processing of pain signals by the brain and spinal cord can cause neuropathic pain.

Nerve pain is characteristically associated with an area of altered sensation, and can be burning, stinging, or shooting in nature. Children/young people may complain the area is hot or cold and may be relieved by rubbing or squeezing the site of pain. This pain is only partially relieved by opioids, although opioids should still be given as first line. Co-analgesics such as amitriptyline, gabapentin (or pregabalin) may be helpful in this situation. Each drug needs to be titrated to maximum benefit. In addition, a steroid pulse may also be helpful if the pain is due to nerve compression. Other complex approaches including use of Ketamine, opioid rotation to methadone (under specialist palliative care supervision only) and local or regional nerve blocks may be used in difficult cases, with advice from the PTC.

12.5.3 Management of pain

In pain management it can be helpful to combine a variety of approaches. Advice should be sought from the specialist team when pain is complex and unresponsive to treatment.

12.5.3.1 Approaches to Pain Management

<table>
<tr><td colspan="2">Treatment of underlying disease
Radiotherapy
Chemotherapy
Surgery</td></tr>
<tr><td>Pharmacological management of pain
Analgesic agents
Sucrose – in under 2-year-olds
Non opioid analgesics
Opioid for mild to moderate pain
Opioid for moderate to severe pain NSAIDs
Antidepressants) for neuropathic
Anticonvulsants) pain

Anaesthetic agents
Local agents e.g., EMLA, Ametop, Menthol Cream, Sedating agents
Inhaled anaesthesia e.g., nitrous oxide
Regional blocks
Epidural
Topical Lidocaine patch</td><td>Non-pharmacological management of pain
Psychological
Education
Explanation
Distraction
Relaxation
Hypnosis

Physical
Warmth e.g. hot water bottle Cold e.g. ice pack
Massage
Physiotherapy
TENS
Acupuncture</td></tr>
</table>

The World Health Organisation (WHO) has recently updated its proposed standard approach to paediatric pain management (see ‘Persisting pain in children with a medical illness’).

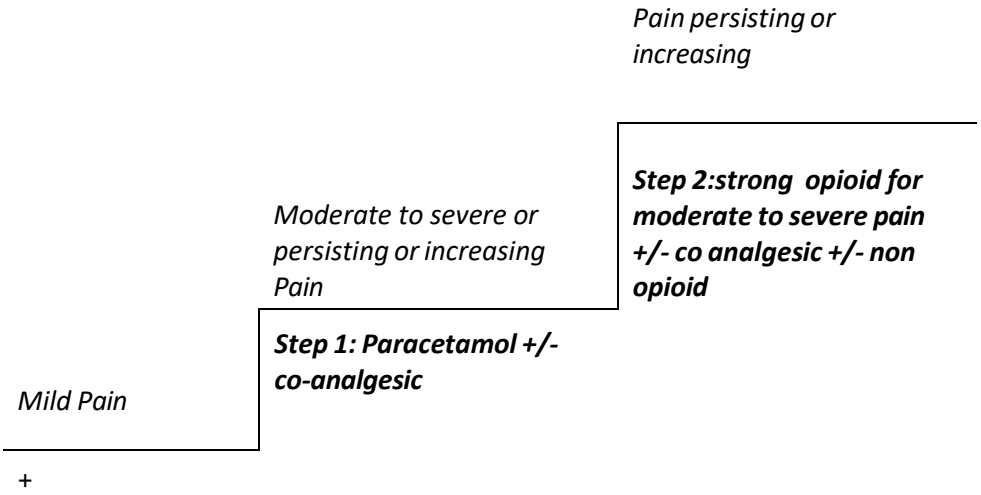
12.5.3.2 WHO approaches to paediatric analgesia

Analgesic drugs	*AND*	analgesic therapy
- by the ladder		-supportive
- by the clock		-behavioural
- by the mouth		-physical
- by the child		-cognitive

12.5.3.3 Analgesics

Although a variety of approaches to pain management are used, analgesics still form the backbone of any strategy. The principles of analgesic use are outlined below.

In most situations, analgesics of gradually increasing strength are used, according to the WHO analgesic ladder (see below). MHRA recommendations have removed step 2 from the WHO ladder, which in essence means removal of the weak opioid step for non-acute pain. The MHRA guidelines suggests that codeine should not be prescribed in <12-year-olds and should only be prescribed in 12–18-year-olds for up to three days with acute pain if pain cannot be relieved by paracetamol / ibuprofen. It is essential that analgesics on all steps are given regularly, and that compliance is checked before moving on to the next step of the ladder. Paracetamol is helpful in mild to moderate pain and has few side effects. The prescriber should be cautious in the use of NSAIDs in patients with low platelets. When pain is no longer relieved by regular paracetamol, a strong opioid at the lowest standard starting dose is recommended. Anticipated side effects are constipation (laxatives should be prescribed routinely) and an antiemetic should also be prescribed for the first 3 days, on an as required basis, due to the risk of nausea and vomiting. In a situation where pain is improving because of other interventions e.g., adjuvant radiotherapy or chemotherapy, analgesics should be reviewed and reduced and/or changed to those on a lower step on the ladder.



Prescribing analgesia

In most situations pain is constant, and analgesics should be given regularly ('background analgesia'). Further analgesia should always be prescribed on a as required. basis ('breakthrough analgesia') for relief of pain between the regular doses of analgesia. If a patient is requiring multiple doses of breakthrough over a prolonged period (e.g., 48hrs) the dose of background analgesia should be increased. The team at the Paediatric Oncology Centre / PTC should be consulted if any problems are encountered.

12.5.3.4 Opioids

Morphine is still the first line for moderate to severe nociceptive pain. Adjuvants or alternatives may need to be considered, particularly, in neuropathic, bone and abdominal (especially liver) pain. Morphine sulphate should be administered four-hourly (immediate release preparations) for breakthrough pain and on initial commencement of Morphine, and twelve-hourly (slow-release preparations) for background pain, calculated from the breakthrough requirement doses, where children can swallow whole solid dose forms. As of 2020, MST granules have been discontinued and at present there is not an appropriate modified release opioid formulation for children unable to swallow whole solid dose forms. The initial dose should be calculated according to the child's weight and then increased, in increments, to provide adequate analgesia. Commencing lowest standard starting dose of morphine for the opiate naive either as a step from Paracetamol or to relieve moderate/severe pain, may be considered appropriate as per BNF-c dose. Titration of morphine can occur as usual based on clinical effect. For pain relief there is no ceiling 24-hour morphine dose. When using the slow-release preparations provide an immediate release preparation for breakthrough pain (10% of the 24-hour morphine dose is now considered a more appropriate initial guide to breakthrough dosing).

Side effects of opioids

Opioids have many side effects. The side effect most likely to cause clinical problems is constipation, and laxatives should always be prescribed concomitantly. Nausea and vomiting are less frequent side effects (but can occur in up to 50% of cases) and antiemetics should be prescribed for the first three days. If the nausea and vomiting has dissipated, then the antiemetic can be stopped. Drowsiness is also common when initiating opioids or when escalating doses but almost always wears off within two or three days. It is useful to warn child/young person and their parents about this or they may worry that the disease has suddenly progressed. Some children/young people experience itching; this usually also wears off but if not antihistamines or 5HT3 antagonists are helpful. If itch persists, then an opioid switch should be considered. Itch is usually more prevalent with morphine and generally less likely to occur with other opioids.
Respiratory depression does not appear to cause problems in children being treated with opioid drugs for pain who are appropriately prescribed and appropriately titrated doses. Children on opioids should be regularly assessed and reviewed.
Once established, opioids should not be stopped abruptly as this may cause an acute withdrawal syndrome; the dose should be reduced gradually (whilst monitoring for withdrawal) and then stopped.

Parental concerns about opioids

Sometimes parents are reluctant to consider the use of morphine for their child's pain. In order to overcome this, the reason for their concern needs to be explored. Often it is not the use of morphine itself that is the problem, but the fact that it represents an acknowledgement that the child is seriously ill/dying. Parents may also be confused about the risk of addiction and may need reassurance that psychological addiction does not occur in children requiring opioids for pain. It may be helpful to point out that morphine can be reduced and stopped should the pain be relieved by other measures such as radiotherapy.

Familiar analogies to explain dependence, tolerance, and addiction (Cooper 2000)

Parents familiar with the habit of drinking coffee in the morning are aware they will experience noticeable effects without usual caffeine intake and are also aware they can withdraw from coffee by gradual lowering of daily consumption. The fact that their body is used to a certain amount of caffeine at certain times of the day means they are dependent.
Many people become accustomed to a certain level of salt for food to taste 'salty'. After a while they may need to increase their salt intake to ensure food continues to taste the same because the body has adjusted to or now tolerates the previous amount of salt, so it no longer has the same effect.

In the same way a child can become tolerant to an opioid dose, so they require a higher dose to achieve the same pain reduction. Tolerance and dependence do not equal addiction

Alternative Opioids

If you consider the patient to be intolerant to morphine and need to discuss the use of alternative oral opioids, please contact the Paediatric Treatment Centre (PTC).

Alternative routes of administration

If the oral route is not possible, for example because of nausea and vomiting, difficulty swallowing, or gradual loss of consciousness, other routes should be considered:

- ***Transdermal***

Transdermal fentanyl is suitable for children who are on a stable dose of opioid, and who dislike or cannot tolerate oral medication. It is not suitable for children in whom pain is changing and whose analgesic needs are therefore altering on a day-to-day basis. It may not be suitable for children on very high doses of opioids because reliable dose conversion becomes difficult, and in small children the available skin surface area may limit number of patches that can be administered.

- ***Rectal***

During the palliative care phase some children tolerate rectal medication and may prefer it to routes involving needles. When a child is no longer conscious (or during the last few hours) morphine suppositories can be used (these are not routinely available so would have to be ordered via your pharmacy). The rectal route may not be suitable for children during curative chemotherapy who may be neutropenic or thrombocytopenic.

- ***Parenteral***

Analgesics can easily be given parenterally by continuous infusion. If a central intravenous catheter is in situ, this can be used, otherwise a needle can be placed subcutaneously. The site of a subcutaneous needle should be changed according to clinical need to avoid inflammation, and topical anaesthetic such as EMLA/Ametop can be used when the needle is re-sited if required. For the older child/young person a Patient Controlled Analgesia infusion pump (PCA) may be used and for younger children a NCA (Nurse controlled analgesia) may be considered. Community PCAs and PPCAs (patient proxy-controlled analgesia) are now available from some specialist services.

- ***Epidural***

Epidural analgesia/anaesthesia can give very effective pain relief but is reserved for pain resistant to other measures and needs specialist management and care.

- ***Buccal***

Buccal administration can provide rapid and effective pain relief, achieving potentially higher systemic concentrations than oral administration. In paediatric and adolescent practise there are very few drugs licensed for buccal administration, and so in practise most medication administered in this way will be unlicensed or off label. Please contact the PTC prior to initiation of buccal therapy to ensure buccal medication delivery is achievable.

12.5.3.5 Management of acute (procedure-related) and persisting pain ON Systemic Anti-Cancer Therapy (SACT), targeted therapy or radiotherapy treatment

On treatment includes children & young people on any chemo, targeted therapy or radiotherapy. Each family should be given an appropriate level of education and support regarding pain management supplemented by a patient information leaflet (PIL) on managing pain in children.

Step 1	**Pain management for out-patients/day case attenders / patients at home** Assess the child, consider the cause of pain Check temperature prior to each dose: ***Give Paracetamol for pain (irrespective of neutrophil count) if***: ▪ The child is afebrile but otherwise well ▪ Pain assessment score: Mild (1-4) or moderate (5-7) and ▪ Check the temperature prior to each dose. If more than 2 doses are needed for pain in 24 hours or a dose needs to be repeated after 4 to 6 hours, for pain, ensure that the child or young person has a pain review by a trained doctor or nurse practitioner for assessment and further management. **Pain management for in-patients (until discharge)** Assess the child, consider the cause of pain Check temperature prior to each dose: ***Give Paracetamol (irrespective of neutrophil count) if***: ▪ The child is afebrile but otherwise well ▪ Pain assessment score: Mild (1-4) or moderate (5-7) and ▪ A child on the ward may be given Paracetamol regularly provided they are receiving appropriate TPR monitoring and assessment by a trained doctor/nurse practitioner. ▪ The child is afebrile but otherwise well For inpatients who are already on antibiotics as per neutropenic sepsis protocol, child can be given paracetamol as antipyretic or analgesic. In this situation there is no need to withhold paracetamol (irrespective of temperature or neutrophil count).
Step 2	**For inpatient, daycare attending and outpatient review** Give ***Morphine*** (or ***Oxycodone*** if morphine intolerant) if: ▪ The child does not meet the criteria in step 1 ▪ Pain has not responded to Paracetamol ▪ The child's pain persists beyond 3 days ▪ Pain assessment score: severe (8 -10) For prescribing Morphine, follow the lowest standard starting dose in the BNF-c. Some clinicians may want to prescribe morphine starting at the lowest starting dose as recommend by BNF for children and then titrate accordingly. A child, with pain persisting on Opiates for longer than three days, should be seen by a trained doctor or nurse practitioner for assessment and further management. For patients with bone tumours, NSAID's (see Section 12.5.3.6) can be used as second line analgesia instead of low dose oral morphine. Discuss with PTC/UCLH.
On- going Opiate use >3 days	If child requires Morphine/Oxycodone for more than 3 days, then the child should have: ▪ A clear on-going management plan with regular follow-up should be implemented. ▪ A child can only continue regular opiates with the agreement of the child's lead consultant (shared care or oncologist) ▪ Awareness of indications for immediate release (IR) and Modified release (MR) use, side effects, tolerance, addiction and withdrawal and alternative routes of administration e.g., transdermal.

12.5.3.6 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

For patients with bone tumours, NSAID's can be used as second line analgesia instead of low dose oral morphine. Discuss with PTC/UCLH.

Other than UCLH patients with bone tumours, NSAIDs are generally avoided in haematology/ oncology patients. This is because of concerns with increased risk of bleeding as a result thrombocytopenia. Therefore NSAID is generally avoided if a patient is predicted to be thrombocytopenic in the near future (e.g. if a patient with normal blood counts is due to start a block of chemotherapy). In this situation, NSAIDs are only used at PTC consultant's discretion (ensure patients requiring NSAIDs are provided gastric protection e.g., lansoprazole / omeprazole) or if there is a local policy stating otherwise.

12.5.3.7 Pain Management OFF Treatment (ie with sustained count recovery):

Step 1	-Assess the child and consider the cause of pain -Give ***Paracetamol*** and/or ***non-steroidal anti-inflammatory drugs (NSAIDs) e.g. ibuprofen*** (see NSAID section at top of this page) if: ▪ Pain assessment score: Mild (1-4) or moderate (5-7)
Step 2	Give ***Morphine*** or ***Oxycodone*** if: ▪ The pain does not respond to Paracetamol/NSAIDs ▪ Pain assessment score: severe (8 -10)
On-going Opiate use beyond 3 days	If a child requires Morphine/Oxycodone for more than 3 days, then the child should be reviewed ▪ A clear on-going management plan with regular follow up should be implemented. ▪ A child can only continue on regular opiates with the agreement of the child's lead consultant (shared care or oncologist) ▪ Awareness of indications for immediate release (IR) and Modified release (MR) use, side effects, tolerance, addiction and withdrawal and alternative routes of administration e.g., transdermal.

12.5.3.8 Management of neuropathic pain

For mild pain (pain scale: 1- 4)	Consider simple analgesia first ▪ Paracetamol if not pyrexial ▪ Ibuprofen if off treatment (see NSAID section above)
For moderate pain (pain scale: 5-7) or **severe pain (pain scale: 8-10)**	Consider a neuropathic agent first line ▪ Gabapentin (titrated up to three times a day dosing over 3 days) or Pregabalin ▪ Amitriptyline (2nd line agent) Consider Morphine during neuropathic pain titration. Opioids should be continued until pain score is <4

12.5.3.9 Bone pain

Non-steroidal anti-inflammatory (NSAID) drugs are particularly helpful for this type of pain but should be used with caution when the platelet count is already likely to be low, as there is an increased risk of gastro-intestinal bleeding. (refer to NSAIDs section at top of this page) Steroids may also be helpful in bone pain and can be administered as a pulse over 3-5 days. Gastric irritation should be anticipated with NSAIDS and/or steroids and a proton pump inhibitor (PPI) prescribed. Pain from discrete bony metastases is often helped by a short course of palliative radiotherapy.

12.5.3.10 Headaches

A headache may have a simple underlying cause. However, headaches from central nervous system leukaemia are most effectively relieved by intrathecal chemotherapy.

12.5.3.11 Pain due to raised intracranial pressure

Symptoms associated with raised ICP include confusion, personality change, drowsiness, vomiting, focal neurology and headache.

Headaches associated with raised intracranial pressure from brain tumours or cerebral metastases may be relieved with steroids. Steroids are often useful as a short-term measure but the disadvantages of long-term steroids, such as mood swings and changes in appearance, usually outweigh the advantages, and treatment with standard analgesics is preferable.
For vomiting the drug of choice is cyclizine. Special consideration should be given if the child/young person has a shunt in situ as the raised ICP could be due to blockage or infection – seek advice from the PTC or paediatric neurosurgical team.

12.6 Dyspnoea

Dyspnoea is not just a symptom of disordered breathing. There is often the combination of physical, psychological, emotional and functional factors. It can impact on a child/young person's day-to-day activities and if severe can be a very frightening symptom for both the child and the carers. Dyspnoea is common in children/young people who have disease in the chest but may be caused by a wide variety of other factors such as anxiety, anaemia, effusions, metastases, infection, SVC obstruction, PE, cardiac failure, central nervous system tumours and liver enlargement. Treatment of potentially reversible causes (complete or partial) where possible, will help alleviate this symptom. Radiotherapy/chemotherapy may be indicated. If anaemia is a significant factor the benefit of blood transfusion should be considered. If bronchospasm is thought to be a contributory factor, a trial of bronchodilators may be helpful. Furosemide may be of benefit in patients with pulmonary metastases. Low dose morphine (30-50% of the analgesic dose for the individual child) can be very effective in reducing the sensation of dyspnoea. Short pulses of steroids are useful for dyspnoea secondary to some types of obstructive mass. In the palliative care setting, Midazolam (buccal) may be useful for reducing the anxiety component contributing to the child's breathlessness.

12.7 Sweating

Sweating is a common problem for children/teenagers with solid tumours, particularly neuroblastoma, and in children with Hodgkin's disease. It is often helped using regular PPI and/or a NSAID such as ibuprofen.

12.8 Seizures

Seizures may occur in children/young people with brain tumours or those with metastatic central nervous system disease. Chemotherapy/radiotherapy could trigger a predisposition to seizures. Reversible causes such as electrolyte imbalances should be investigated and treated appropriately. Occasional, short seizure activity may not require medication, appropriate rescue medications as per APLS guidelines for seizure management should be available.

Regular oral anticonvulsants may be appropriate for children with brain tumours or cerebral/CNS metastases having frequent convulsions over a prolonged period, and levels (where indicated) should be monitored to ensure that they are within therapeutic range.

Seizures can become difficult to control in the terminal phase and in these circumstances continuous subcutaneous/ intravenous midazolam may be helpful.

12.9 Anxiety and Agitation

Anxiety may reflect a child/young person's need to talk about their fears and concerns and may improve following discussion and explanation. Pain as an underlying cause should be considered. Non-pharmaceutical measures are often helpful such as psychological intervention by a suitably qualified team member, play therapist or child psychologist/psychiatrist where available (see Approaches to Pain Management). Sublingual lorazepam or low dose buccal midazolam may be helpful, particularly for panic attacks, episodic anxiety or for procedures likely to cause anxiety.

12.9 Terminal Restlessness

Restlessness and agitation, sometimes termed terminal restlessness, is common in the final stages of life. It can be treated with midazolam, haloperidol or levomepromazine, most are compatible with opioids in subcutaneous/intravenous infusions, but the compatibility of drugs should be checked. Levomepromazine lowers the seizure threshold so is not generally used as first line in children with CNS disease. Haloperidol should be considered if there is a significant hallucinogenic or psychosis component to the agitation. Either Haloperidol or Levomepromazine should be considered if escalating Midazolam doses are not effective.

12.10 Retained Respiratory Tract Secretions

(Often Termed the Death Rattle)

This is a common symptom in children/young people who lose the ability to swallow secretions, and in those with decreased levels of consciousness in the final stages of life. It can be distressing for parents / carers but not necessarily for the child/young person since they are often unconscious at this stage. Early intervention with anti-secretory agents can be of benefit. A hyoscine hydrobromide (scopoderm) patch provides a non-invasive method of treatment but may not be of benefit as the symptom worsens. Subcutaneous/intravenous hyoscine hydrobromide can be used, although as it crosses the blood–brain barrier it may cause neurological side effects and agitation. Glycopyrronium is a useful alternative and may be used whilst the child/young person is still conscious, as it does not cross the blood–brain barrier and can be given orally or via subcutaneous/intravenous infusions. Non-pharmaceutical methods, such as repositioning to avoid pooling of secretions, can be helpful. Oral/pharyngeal suction is sometimes beneficial however excessive suction should be discouraged as it may stimulate more secretions.

12.11 Bleeding

Significant bleeding is uncommon in children/young people. Persistent oozing e.g., bleeding gums can be managed with topical agents such as tranexamic acid or adrenaline 1:1000 applied directly to the bleeding point. If low platelets are a contributory factor, a platelet transfusion should be considered as appropriate.

In the palliative phase a significant bleed is a possibility, and this should be explained to the parents. Medication for anxiety (Midazolam), agitation (Midazolam) and breathlessness (Diamorphine/Morphine) should be made available.

12.12 Syringe Drivers

A syringe driver is an infusion pump used to give continuous medication parenterally, usually over a 24-hr period. Syringe drivers can deliver medication intravenously (e.g. via central venous catheter) or subcutaneously. It is particularly suitable for children who are unable to tolerate oral medication or who require immediate control of difficult symptoms, unresponsive to other intervention. Although it is a common route to administer medication at the end of life, it can also be used for short periods to gain control of difficult symptoms or when the oral route is temporarily impractical (e.g., persistent vomiting).

As recommended by MHRA an anti-syphon extension should be used with any syringe driver.

Indications for using a syringe driver

- Inability to absorb, tolerate or take oral medication
- Difficulty in swallowing
- Persistent vomiting
- Bowel obstruction
- Severe weakness/semi-unconscious state
- Alternative routes not appropriate
- Unsatisfactory response to oral routes
- Patient/parent anxieties

Advantages of using this delivery system are

- Delivers drugs at an even rate continuously, maintaining plasma concentration without peaks and troughs
- May minimise the number of injections required
- Mobility and independence is maintained
- The ability to deliver complex drug combinations safely

Certain drugs can be mixed together and given in the same syringe driver. Others will require the use of a separate syringe driver. The compatibility of drugs should always be checked. In some situations up to 5 drugs can be mixed in one driver. Advice regarding mixing of 3 or more drugs should be sort from the specialist palliative care service.

Notes on using syringe drivers

- It is usual practice to change the syringe every 24 hours
- Discuss with specialist palliative team if the mixing of more than three drugs in one syringe is indicated.
- Check with your own pharmacy or specialist service before using any unusual combinations
- Avoid drug combinations diluted in sodium chloride 0.9% when using cyclizine
- Never use chlorpromazine, prochlorperazine and diazepam subcutaneously

13.

MANAGEMENT OF FLUID AND ELECTROLYTES

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ł These doses are from BNFc and BNF (Oct 2018). If future versions of BNFc/BNF change these to alternative doses, the authors recommend using new doses from newer versions of BNFc/BNF

§ Doses from original 4th edition v1.0. Only use under guidance and direction of experts and specialists

13. Management of fluids and electrolytes

Introduction

Management of fluid and electrolyte imbalance forms an important part of the care of paediatric oncology patients. Although some problems are peculiar to patients with malignancies their management follows general paediatric principles. The chapter has been written to provide uniformity of treatment.

In places the document is quite prescriptive. If the particular preparation mentioned is not available in the hospital pharmacy, local guidelines should be used. Where management of electrolyte imbalance becomes very complex and complicating factors like renal impairment are present, always consult the relevant PTC/PICU/renal/endocrine centres for advice and/or patient transfer.

Calculation of electrolyte and fluid deficits is provided in Appendices A and B for the sake of completion. This protocol is in keeping with APLS guidelines. The information about the use of hypertonic (2.7% commercially available; or 3%) saline has been obtained from the South Thames Retrieval Service clinical guidelines section, including the instructions on how to make it up correctly should this be required. It should be stressed that this should only be administered following discussion with a consultant, and, in the case of a critically unwell child, in liaison with the relevant PICU team.

Causes of fluid and electrolyte imbalance in paediatric oncology

Paediatric oncology patients are at high risk of developing fluid balance abnormalities and electrolyte disturbances. These may occur in the following settings:

- During hyperhydration given as part of standard chemotherapy regimens.
- During induction chemotherapy for acute leukaemia, where hyperhydration is essential for the prevention of acute tumour lysis syndrome.
- As part of treatment of tumour lysis syndrome, characterised by hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia.
- Following nephrotoxic chemotherapy (e.g. cisplatin, ifosfamide),or liposomal amphotericin B which may cause a renal tubular leak, resulting in renal loss of electrolytes, particularly sodium, potassium, magnesium and phosphate.
- As a result of chemotherapy causing vomiting, diarrhoea or mucositis, leading to dehydration, hypokalaemia, hypo- or hypernatraemia, or hypomagnesaemia.
- In post-stem cell transplant patients with gastrointestinal graft-vs-host disease, where fluid and electrolyte loss from the gut may be severe and prolonged.
- In patients with acute septic shock where profound hypotension may require significant fluid resuscitation.
- In febrile patients, in whom insensible fluid losses may be increased.
- In patients with central diabetes insipidis e.g. as a result of a brain tumour (especially craniopharyngioma) or Langerhans Cell Histiocytosis. This may cause dramatic life-threatening intracerebral fluid and sodium shifts unless managed correctly.
- In patients with veno-occlusive disease (VOD) of the liver, most common after stem cell transplant using busulphan-containing conditioning regimens.
- In patients with disseminated malignancy who are at risk of hypercalcaemia.
- Some drugs can cause a syndrome of anti-diuretic hormone secretion (SIADH), with hyponatraemia, e.g. vincristine, carbamazepine.

These guidelines discuss the general management of certain fluid and electrolyte disturbances, and some specific scenarios. Topics where the fluid and electrolyte management is covered as part of a section within another chapter of these guidelines have been cross-referenced rather than repeated here. These include: Hyperhydration for the prevention and treatment of tumour lysis syndrome, Septic shock and Veno-occlusive disease.

Electrolyte Disturbances

Sodium

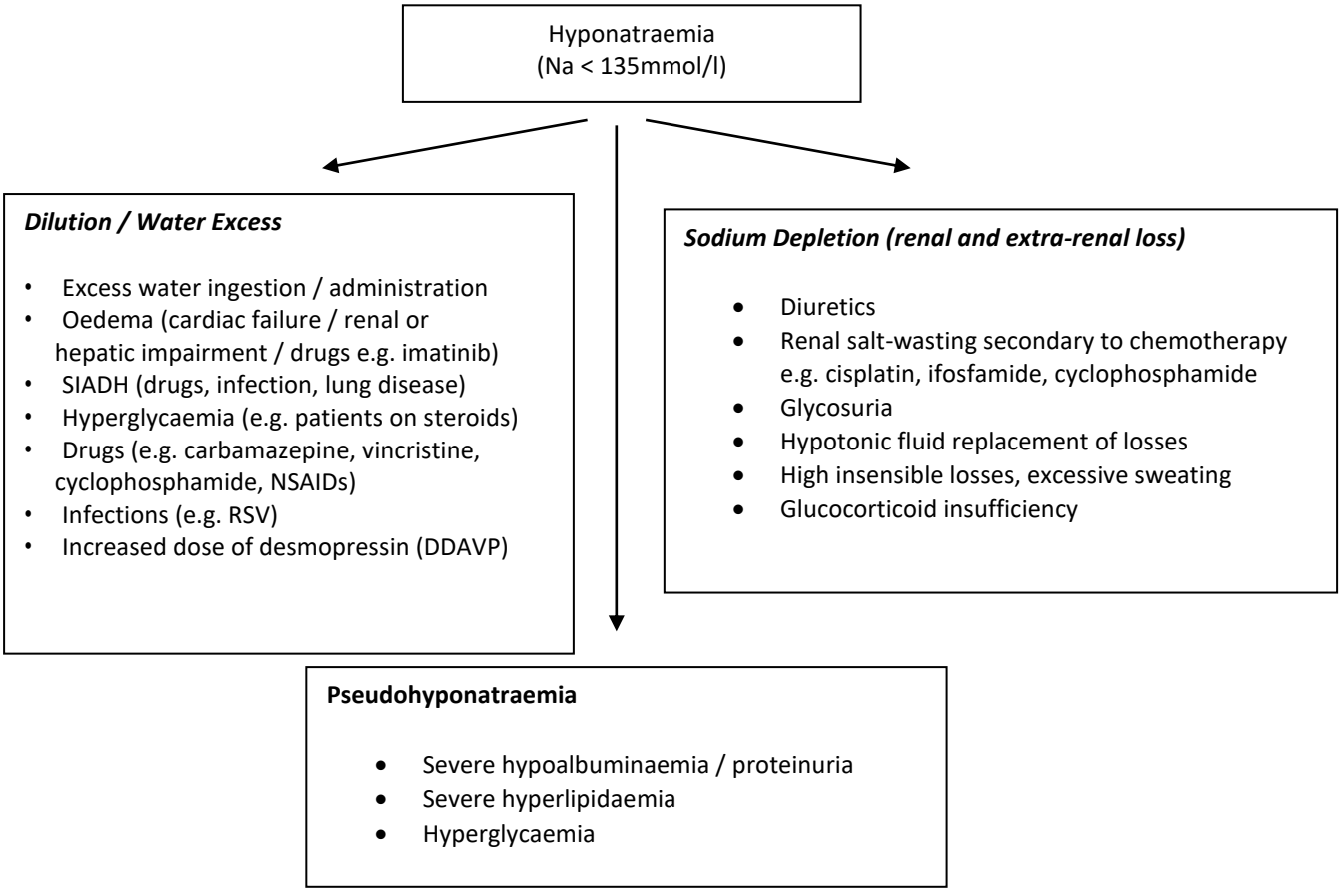
Sodium is the major extracellular cation. Its movement is, therefore, inextricably linked to that of water. Disorders of sodium are predominantly those of dehydration/under-hydration, or overhydration, and thus management is largely linked to management of fluid balance.

Hyponatraemia

Definition: Na < 135mmol/l (mild 130-134mmol/l; moderate 127-129mmol/l; severe ≤ 126mmol/l)

Clinical features: asymptomatic in mild and sometimes moderate cases; nausea, lethargy, headache, altered level of consciousness, seizures.

Figure 13.1 Causes of Hyponatraemia



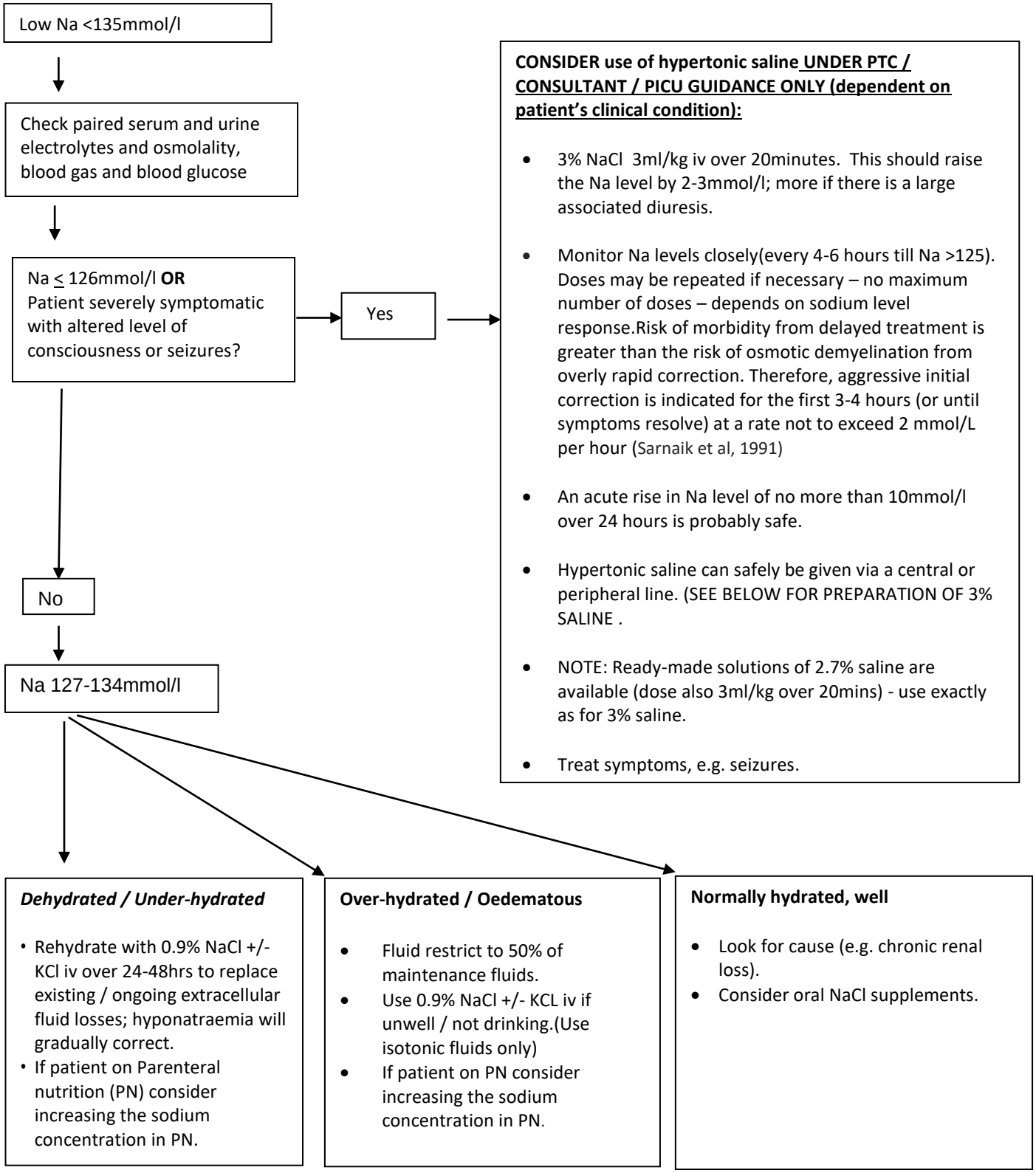
Fluid Overloaded	Euvolaemic	Dehydrated

• **IV fluid administration in excess of the child's needs**
• Nephrotic syndrome
• Cirrhosis
• Heart Failure
• Acute/ Chronic Renal Failure
• Obstructive uropathy
	• **Administration of enteral hypotonic fluids** (including dilute formula, Oral Rehydration Solutions, excessive water intake)
	• Psychogenic Polydipsia
	• **Increased ADH secretion**
	  • **Pulmonary: pneumonia, bronchiolitis, mechanical ventilation**
	  • **CNS: infections, injury, tumour**
	  • **Post-operative, trauma, pain**
	  • Endocrine: Hypothyroid, low cortisol
	• Medications
	  • Chemotherapy (cyclophosphamide, vincristine, platinum based agents)
	  • Antiepileptics (valproate, carbamazepine, oxcarbazepine)
	  • Vasopressin
		• **GI losses and rehydration with free water**
		  • Gastroenteritis
		  • Secretory/osmotic diarrhoeas
		  • Ostomies
		• Skin losses (CF / burns)
		• Abdominal 3rd spacing
		• High rate fluid consumption post exercise
		• Hyperglycaemia
		• Renal Losses
		  • Thiazide Diuretic
		  • Cerebral salt wasting
		• Primary renal Tubular Disorders
		• Hypoaldosteronism
		• Metabolic alkalosis

Management of hyponatraemia

- **Acute** — <48 hours. More likely to be symptomatic and are at risk for complications, as there has not been sufficient time for cerebral adaption to occur.
- **Chronic** — >48 hours, cerebral cell volume adaptation has likely occurred hence less likely to be symptomatic and more importantly are at-risk for osmotic demyelination if hyponatremia is corrected too quickly.
- The target rate of serum sodium correction is 6-8mmol/L in 24 hours (unless seizing- see flow chart below). (Sterns RH 2018)
- All children should have a strict fluid balance including weight (minimum daily, but maybe 12 hourly for more unwell children).
- Remember to treat the underlying cause.

Figure 13.2 Management of hyponatraemia



NOTE: Management of hyponatraemia depends very much on the clinical condition of the patient and the likely underlying cause, rather than merely the absolute sodium value.
Chapter 6 on management of raised intracranial pressure

Hypertonic saline (2.7% or 3% saline)

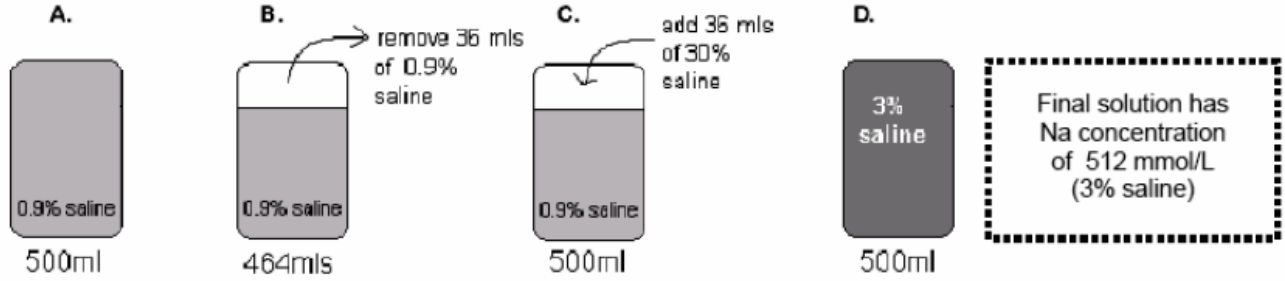
In addition to being used for the treatment of severe hyponatraemia or symptomatic hyponatraemic seizures, hypertonic saline is also used for the treatment of cerebral oedema and raised intracranial pressure, with some advantages over mannitol (see Chapter 6 on management of raised intracranial pressure).

Intravenous hypertonic saline induces a shift of fluid from the intracellular to the extracellular space across the osmotic gradient it generates. It therefore reduces brain water, increases blood volume and increases plasma sodium. Note that intracellular volume is inversely proportional to plasma sodium concentration.

Rapid correction of hyponatraemia can result in osmotic demyelination syndrome which manifests as irreversible neurologic features (dysarthria, confusion, obtundation and coma) which often present days after sodium correction (Aegisdottir et al. 2019).

Figure 13.3 Preparation of 3% Saline using 30% Saline

NB! Use commercial 'ready-made' hypertonic saline solutions (2.7%) if available in preference to mixing 3%, to reduce the risk of drug preparation errors. They are almost identical and should be used in the same way.



DO NOT connect the 500ml bag of 3% saline directly to the patient's iv line (RISK OF SERIOUS ACUTE SODIUM OVERLOAD IF ENTIRE BAG IS ACCIDENTALLY INFUSED.) ALWAYS withdraw the prescribed dose of 3% saline (eg 3ml/kg) and administer to patient separately.

In case of accidental overdose of 3% saline:

- Disconnect 3% saline infusion immediately and contact PICU for advice.
- Give ł 1mg/kg iv frusemide immediately, aiming for a natriuresis of 6ml/kg/hour, which may be enough to keep Na level within the safe range.
- Measure plasma Na every 30-60 minutes for trend. (Indications for dialysis include oliguria, anuria or Na level rising rapidly ie >5mmol/hour.)
- **DO NOT** attempt to correct Na with free water or use 0.45% saline (risk of sudden drop in brain osmolality).

Hypernatraemia

Definition: Na >145mmol/l (and usually not symptomatic/problematic >150mmol/l).

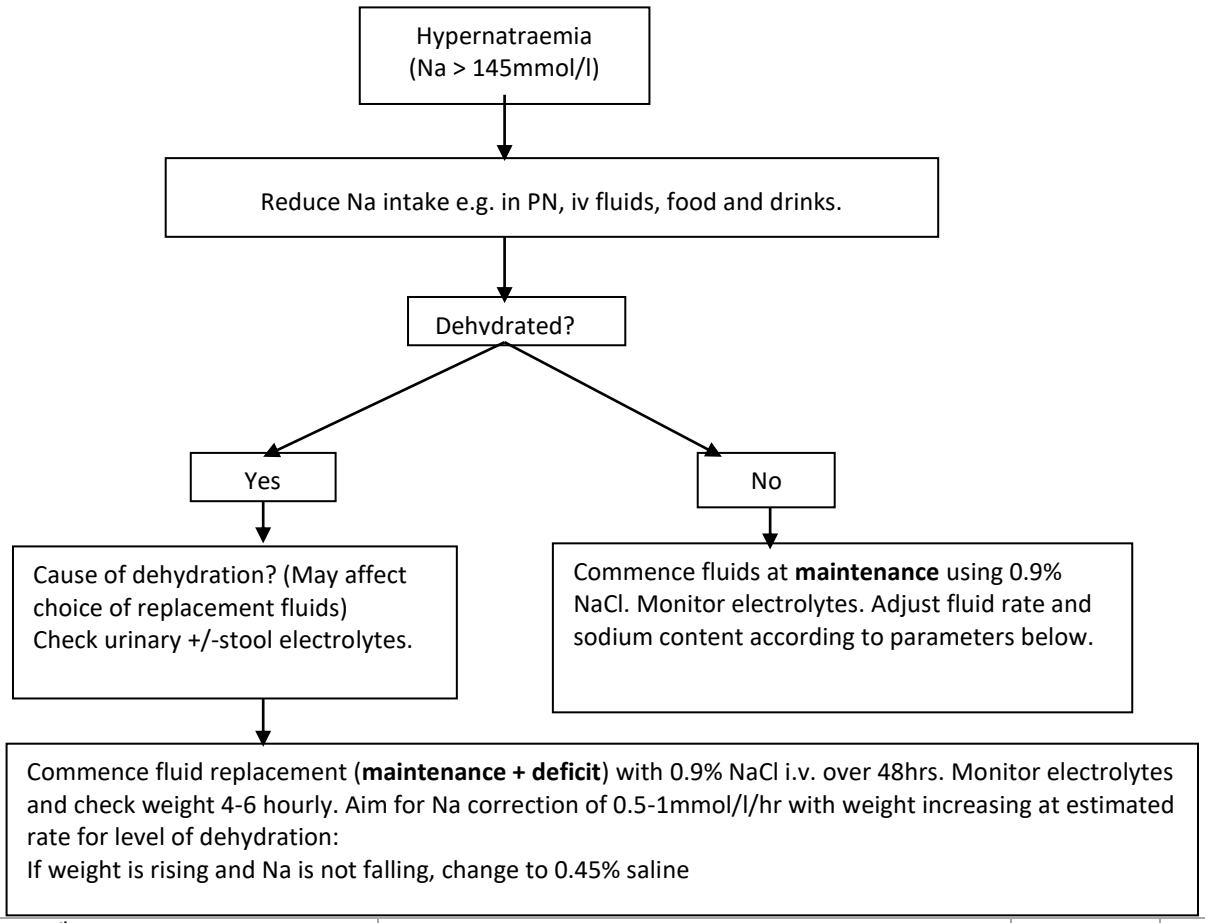
- Moderate to severe hypernatraemia can cause acute brain shrinkage with vascular rupture, haemorrhage, demyelination and permanent neurological injury
- Infants and small children are more vulnerable to hypernatraemia due to greater insensible losses and inability to communicate their need for fluids or access fluids independently. (Somers and Traum, 2020)

Clinical features: symptoms and signs of dehydration; alter
ed level of consciousness, seizures.

Causes: Usually due to water loss rather than sodium excess:

- Diarrhoea
- High insensible fluid losses
- Water deprivation
- Diabetes insipidis (central or nephrogenic), omission of desmopressin (DDAVP)
- Obstructive uropathy
- Excess sodium administration / iatrogenic

Figure 13.4 Management of hypernatraemia



Potassium

Hypokalaemia

Definition: K< 3.5 mmol/l (with/without ECG changes)

Clinical features: Usually asymptomatic. Muscle weakness, lethargy, paralytic ileus, decreased deep tendon reflexes, rhabdomyolysis.

ECG changes (normally occur when K < 2.5mmol/l): ST segment depression, small T-wave amplitude, U waves, prolonged QT and arrhythmias including ventricular tachycardia, ventricular fibrillation or Torsades de Pointes.

Causes:

- Inadequate intake
- Renal loss e.g. diuretics, renal tubular leak secondary to disease or drugs
- Gastrointestinal loss (diarrhoea & vomiting)
- Sepsis
- Steroids
- Primary or secondary hyperaldosteronism (salt & water are retained)
- Skin loss via excessive sweating / insensible losses
- Shifts from extracellular to intracellular compartments may be caused by alkalosis, hyperglycaemia,DKA, insulin, B-adrenergic agonists, e.g. salbutamol.
- Drugs eg ?penicillins, amphotericin B, cisplatin, adrenaline
- Bicarbonate

In patients receiving hyperhydration for tumour lysis prevention or treatment, low K should **not** be corrected until symptomatic and even then, only on discussion with consultant, since total body potassium is likely to be high rather than low.

Consider:

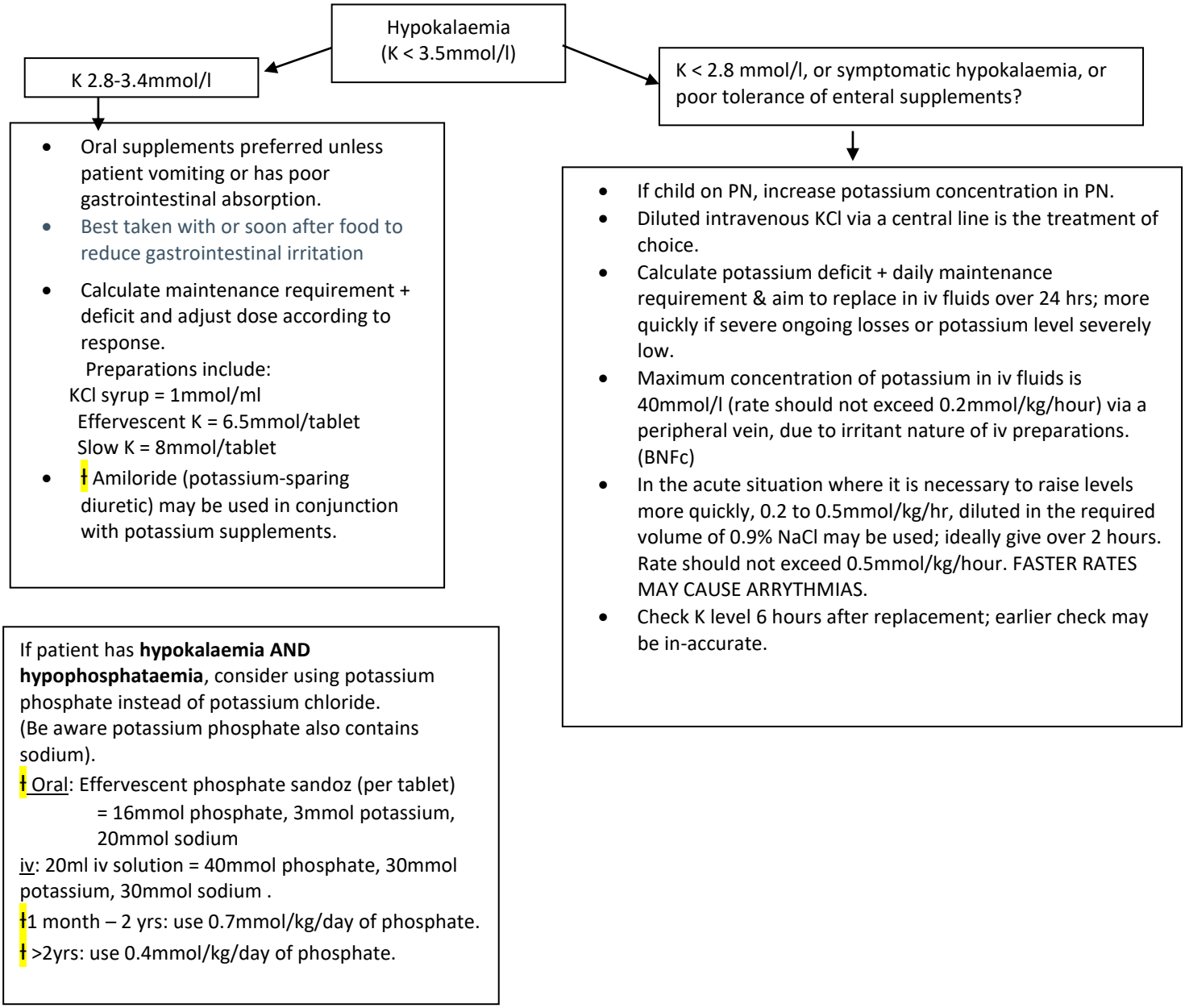
- repeat electrolytes to verify the initial result

Note: serum potassium level can be falsely elevated in haemolysed/finger prick samples, so a venous sample should be taken if clinical suspicion of hypokalaemia

- baseline renal function
- blood gas if concerns regarding acid-base status
- serum magnesium level, especially if hypokalaemia is refractory to treatment (hypomagnesaemia promotes potassium wasting)

If hypokalaemia is severe, or child unwell, always check acid-base status

Figure 13.5 Management of hypokalaemia



Hyperkalaemia

Definition: K > 5.5mmol/l (with/without ECG changes)

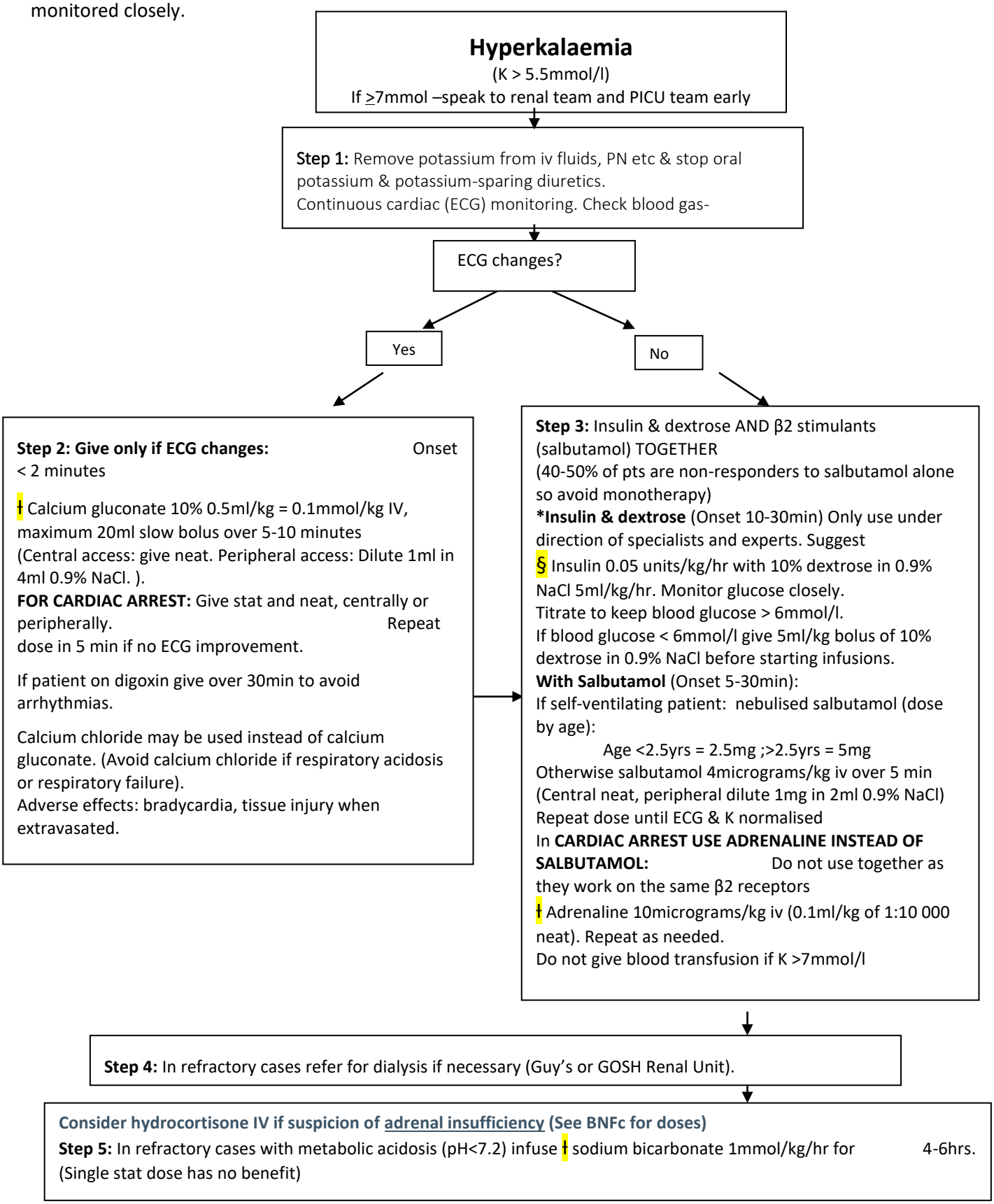
Clinical features:
Muscular weakness reduced deep tendon reflexes, paralytic ileus, abdominal pain, respiratory paralysis, cardiac arrythmias / arrest (most common at K levels > 7.5mmol/l). Features of the underlying cause, e.g. renal failure, may be apparent.
ECG changes: Peaked T-waves > 5mm tall, decreased QT interval, short PR interval (becoming prolonged as K level rises), wide QRS complexes, broad & flat P-waves, ST changes, bradycardia, ventricular fibrillation or asystole.

Causes:

- Beware of pseudohyperkalaemia e.g. traumatic haemolysed samples, delay in analysis, contamination with EDTA and tumour lysis with cell breakdown in the sample tube
- Tumour lysis syndrome at start of chemotherapy is a haematological emergency.
- Potassium overload / iatrogenic: in iv fluids, PN, drugs (penicillins), transfusions.
- Reduced potassium excretion e.g. renal failure, adrenal insufficiency, potassium-sparing diuretics (spironolactone, amiloride), drugs (e.g. ciclosporin).
- Catabolic states wherein K is released from cells e.g. haemolysis, acidosis.
- Drugs causing shifts from the extracellular to intracellular fluid compartments e.g. B-blockers, suxamethonium.
- eg NSAID, trimethoprim, heparin, chemotherapy, K-sparing diuretic, ACE inhibitor, digoxin, mannitol
- Hyperglycaemia
- Haemolytic Uraemic Syndrome

Figure 13.6 Management of hyperkalaemia

Generally speaking, a potassium level between 5.0 and 5.5 mmols/l need not be treated acutely but rather monitored closely.



** NICE evidence search:* *Optimal Dose and Method of Administration of Intravenous Insulin in the Management of Emergency Hyperkalaemia: A Systematic Review* *Source: PubMed - 01 January 2016 - Publisher: Plos One*

- Consider Polystyrene sulfonate – per rectal (PR) or oral (with lactulose). This should only be used under subspecialist guidance (eg nephrologists). If unable to obtain subspecialist guidance or if clinical team is not familiar with this drug, then do not use. Caution or avoid if ileus, recent abdominal surgery, perforation, hypernatraemia. (Discuss with subspecialists) Onset of Action: 1 hour PR, 4-6 hours oral. Doses as per BNFc Calcium polystyrene sulfonate | Drugs | BNFC | NICE (last read 24/1/2023)

Calcium

Calculate the corrected calcium for serum albumin concentration:

Corrected Calcium = Measured Calcium + {(40 – serum albumin) x 0.02}

Hypocalcaemia

Definition: Corrected Ca < 2mmol/l

Clinical features: weakness, cramps, tetany, seizures, hypotension, and cardiac arrythmias.

ECG changes: If severe - prolonged QT, pulseless electrical activity (PEA), ventricular fibrillation

Causes: May be part of any severe illness, e.g. septicaemia.

- Tumour lysis syndrome
- Pancreatitis (e.g. caused by asparaginase)
- Acute or chronic renal failure
- Citrate infusion (e.g. in massive blood transfusions), post autologous or allogeneic stem cell infusion

Management: Treatment should be considered if patient is symptomatic.

IN THE SETTING OF TUMOUR LYSIS, CALCIUM MUST NOT BE GIVEN AS RENAL FAILURE MAY BE PRECIPITATED.

(Phosphate binders & haemofiltration / dialysis may be required in this situation - discuss with consultant on call and renal team, especially if phosphate >2mmol/l.)

Treat underlying cause.

In an arrest situation calcium gluconate (10%) 0.5ml/kg may be given stat and neat.

Otherwise, give as an intravenous slow bolus: calcium gluconate (10%) (BNFc doses)

Can also use calcium chloride (10%) (BNFc doses)

Oral calcium gluconate (BNFc doses)

Hypercalcaemia

Definition: Corrected Calcium > 2.7mmol/l

Clinical features: may be asymptomatic or present with anorexia, malaise, polyuria, abdominal pain, vomiting, weight loss, failure to thrive, renal calculi/colic, hypertension, behavioural disturbances.

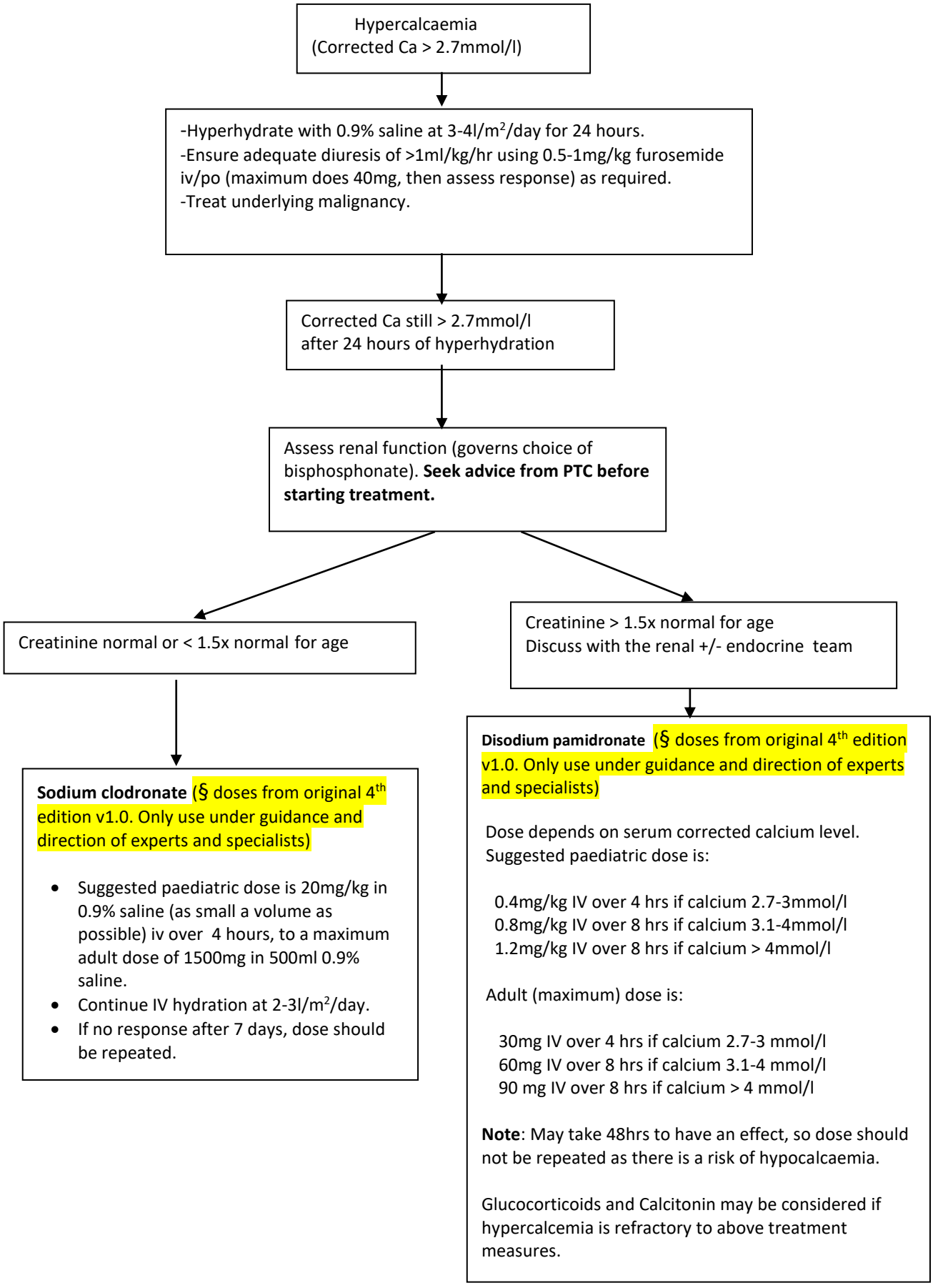
ECG changes: short QT, other arrhythmias

Causes:

- Disseminated malignancy
- Idiopathic / iatrogenic e.g. thiazide diuretics
- Hyperparathyroidism
- Excess vitamins A or D
- Post rhabdomyolysis

Management: Isolated hypercalcaemia in the absence of symptoms may not require treatment. Treatment is required if **corrected calcium** level > 2.7 mmol/l and/or patient is symptomatic. Treatment may be inappropriate in patients with progressive refractory malignancy in the palliative care setting.

Figure 13.7 Management of hypercalcaemia



Magnesium

Hypomagnesaemia

Definition: Mg < 0.6 mmol/l +/- ECG changes

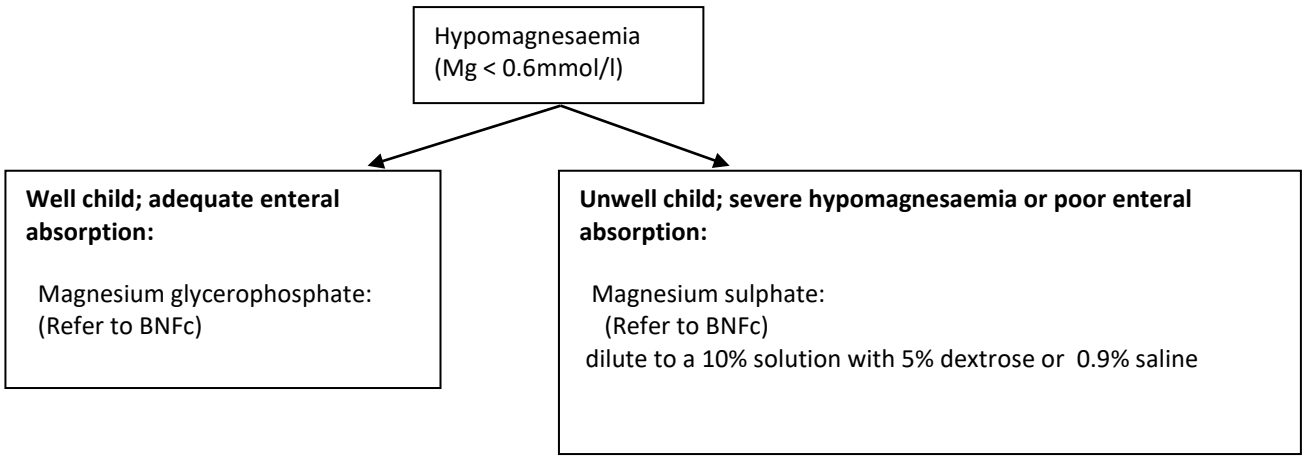
Clinical features: may be asymptomatic; severity of symptoms may not correlate with serum Mg level. Hypertension, anorexia, nausea, vomiting, lethargy, weakness, hyperreflexia muscle tremors/fasciculations/cramps/weakness, paraesthesia, irritability, confusion, seizures. Often occurs in conjunction with hypocalcaemia or hypokalaemia.

ECG changes: Arrhythmias PR/QT prolongation eg Torsades

Causes:

- Diarrhoea
- Renal tubular leak, particularly in post-BMT patients.
- Pancreatitis (e.g. secondary to asparaginase)
- Drugs (e.g. amphotericin, aminoglycosides, cisplatin, tacrolimus, ciclosporin, pentamidine, diuretics, laxatives, chronic PPI use)
- TPN
- Poor magnesium intake

Figure 13.8 Management of hypomagnesaemia



Hypermagnesaemia

Definition: Mg > 2mmol/l +/- ECG changes

Clinical features: nausea, muscle weakness, hyporeflexia, sedation, hypoventilation, respiratory acidosis, hypotension (due to vasodilatation), bradycardia, arrythmias, and respiratory paralysis.

ECG changes: Arrhythmias, bradycardia, heart block

Causes:

- Increased intake of magnesium supplements (especially in renal impairment)
- Rhabdomyolysis
- End-stage renal failure
- Adrenal insufficiency

Management:

Remove cause of elevated Mg levels. Infusion of calcium produces a short-lived reduction in serum Mg, but often improves clinical condition dramatically.

Calcium gluconate (10%) ŧ 0.07mmol/kg over 5-10 min or as a 24-hr infusion 0.2 mmol/kg/hr (via central line, as it is an irritant.)

Can also use calcium chloride (10%) ŧ 0.2 mmol/kg iv slow bolus (<12yrs)
ŧ 5-10 mmol iv slow bolus (>12yrs)

Ensure adequate rehydration and force diuresis with frusemide 0.5-1mg/kg (maximum 40mg) if urine output < 1ml/kg/hr . Dialysis may be required if unable to diurese adequately.

Phosphate

(Refer to the tumour lysis management guidelines for the normal serum values of phosphate according to age)

Hypophosphataemia

Definition: Phosphate <1 mmol/l. Clinical symptoms usually starts when level is < 0.64mmol/l). Levels < 0.3mmol/l life threatening.

Clinical features: Irritability, disorientation, tremors, seizures, haemolytic anaemia, reduced myocardial function, potential respiratory failure, potential coma

Causes :

- Inadequate intake,
- Decreased absorption or increased losses from the gastrointestinal tract
- Increased renal phosphate excretion.
- Refeeding syndrome

Management:

Identify the underlying cause and take steps to correct it.
Replacement is generally done very slowly because the actual serum level may not reflect a deficit in the intracellular compartment.
Unless acute symptoms are present, phosphate depletion is treated by enteral administration of phosphorus: up to 6mmol/kg/day divided into several doses to minimize diarrhoea.
Parenteral administration of phosphates is usually restricted to children with levels below 0.3mmol/l: 0.15-0.33 mmol/kg as a continuous infusion over at least 6 hours. Either potassium phosphate or sodium phosphate may be used, with the potential associated complications associated with hyperkalaemia or hypernatraemia.
Other adverse effects of phosphate administration include hyperphosphataemia, which may result in hypocalcaemia, and hypotension. It must be well diluted to avoid irritation of the blood vessels, extravasation, or infiltration leading to tissue necrosis. Administration of large quantities of phosphorus may lead to precipitation with calcium if levels are not carefully monitored

Hyperphosphataemia

Definition: Phosphate >1.4mmol/l)

Clinical features: tachycardia, hyperreflexia, abdominal cramps, nausea, diarrhoea, muscle tetany

An inverse relationship exists between phosphorus and calcium in the extracellular compartment. Therefore in conditions producing hyperphosphataemia, hypocalcaemia also exists. The relationship between these two imbalances accounts for the fact that the clinical signs and symptoms associated with hyperphosphataemia are the same as those found in the child with hypocalcaemia.

Causes :

- Chronic renal failure
- Tumour lysis

Management:

Adequate hydration/hyperhydration, diuresis
Aluminium antacids
For hyperphosphataemia due to renal failure, sodium bicarbonate may be used.
Correction of hypocalcaemia in children who do not have tumour lysis.
In refractory cases renal dialysis may be required. .

Specific Fluid Balance Problems in Oncology Patients

Diabetes Insipidus

In paediatric oncology this is seen most frequently in the setting of patients with brain tumours (especially craniopharyngioma) or Langerhans Cell Histiocytosis (LCH). These patients tend to have central rather than nephrogenic diabetes insipidus, as a result of disruption of the hypothalamo-pituitary axis and consequent reduction in vasopressin (ADH) secretion. This results in the production of large volumes of dilute urine, with the risk of developing either hypernatraemic dehydration or hyponatraemia and water intoxication if not appropriately managed.

Treatment is with desmopressin/DDAVP under the expert guidance of a paediatric endocrinologist who should always be consulted at an early stage.

Children with this condition should have strict fluid balance monitoring whilst in hospital, as well as close monitoring of plasma and urine electrolytes and osmolarity.
Large positive or negative fluid balances should be avoided. If the child starts producing large volumes of dilute urine with a resultant rise in plasma sodium or shows a sudden reduction in urine output with a drop in plasma sodium, desmopressin doses are likely to need adjustment. This should always be done under senior / expert guidance.

Doses of desmopressin as per senior / expert guidance / BNFc.

Hyperhydration for the Prevention and Treatment of Tumour Lysis Syndrome (TLS).

See Chapter 6 on Oncological Emergencies

Septic Shock

See Chapter 3 on Management of Infections

Veno-occlusive disease

See Chapter 6 on Oncological Emergencies.

Chapter 13 - Appendix A

Normal Daily Electrolyte Requirements

Sodium	2-4mmol/kg/day
Potassium	2mmol/kg/day
Calcium	3mmol/kg/day
Magnesium	0.75mmol/kg/day

Calculation of Electrolyte Deficit

Deficit (mmol) = (Normal level – actual level) x Weight (in kg) x 0.7

e.g. a 24kg child with serum potassium of 2.5mmol/l

Deficit = (4-2.5) x24 x 0.7
=25.2mmol

Maintenance = 2mmol/kg/day
= 2 x 24
= 48 mmol

Thus, total requirement = Deficit + Maintenance
= 25 + 48
= 73mmol

i.e. If poor oral intake will need maintenance hydration containing 73mmol over next 24 hours. If taking diet, and hence maintenance electrolytes, needs 25 mmol extra potassium over next 24 hours.

General Rules for Intravenous Electrolyte Administration

iv electrolytes may be put in 0.9% Normal saline, 5% dextrose, or 2.5% dextrose + 0.45% saline.

Magnesium sulphate **and** calcium gluconate or calcium chloride **and** potassium chloride can all be added to the same iv fluid bag if electrolyte concentrations are low (i.e. some cisplatin regimens + PN). If concentrations are too high, calcium sulphate precipitates. Thus at higher concentrations it is safe to mix only 2 supplements, i.e. CaCl & KCl, CaCl & MgCl, Mg SO4 & KCl, because MgSO4 & Ca preparations precipitate.

Chapter 13 - Appendix B

Fluid Balance

Calculation of daily fluid balance is important in all paediatric oncology patients but is essential in those receiving intravenous fluids (especially hyperhydration regimens), post-stem cell transplant patients, those with gastrointestinal losses, those with renal or cardiac abnormalities (e.g. impaired cardiac function following previous anthracyclines), or those who are septic or unwell.

Weight and blood pressure are useful parameters in assisting with fluid balance interpretation. Insensible losses need to be considered in addition to charted fluid losses, so a positive balance on a fluid chart is usually not strictly accurate, as it does not account for these losses. Febrile patients will have higher insensible losses than afebrile patients.

For practical purposes, 1kg of weight = 1 litre of fluid.

No action should usually be taken on the basis of a single parameter. The child should be fully assessed, including BP, heart rate, respiratory rate, capillary refill time, temperature, weight and general condition.

If it is felt necessary to act on a positive fluid balance, a reduction in intravenous fluid rate may be sufficient. Older children can tolerate a larger positive fluid balance than younger ones, and larger patients can tolerate a larger positive fluid balance that smaller patients.

Diuretics should only be used in patients who are in too great a positive fluid balance for their clinical status. The choice of diuretic is frusemide 0.5-1mg/kg intravenously or orally (if intestinal absorption is not impaired) as a single dose, with assessment of subsequent urine output. Adult-sized patients should receive no more than 40mg of frusemide initially, followed by assessment of response. Frusemide may cause renal loss of sodium and potassium; plasma levels should be monitored. Beware of using diuretics in patients who have peripheral oedema but may, in fact, be intravascularly depleted, eg as evidenced by a baseline tachycardia.

Calculation of Fluid Requirements

Normal daily fluid **maintenance** requirement is calculated on the basis of fluid required to keep a patient well hydrated and passing reasonable amounts of urine. The standard calculation (based on APLS recommendations) **includes the following considerations:**

1. Baseline maintenance requirements
2. Replacement of *insensible losses* through sweating, respiration, normal stool loss (usually 10ml/kg in an adult, 20ml/kg in a child & 30ml/kg in a baby <1 year)
3. Replacement of *essential urine output* (=minimal urine output required for waste excretion)
4. Some extra fluid to maintain a modest state of diuresis

Total daily fluid requirement consists of:

Maintenance + Replacement of deficit (existing/on-going loss) + Resuscitation (if required)

Calculation of Maintenance Fluid Requirement

(Includes 1+2+3+4 above)

Body Weight	Fluid Requirement per 24 hrs	Fluid Requirement per hr
First 10 kg	100ml/kg/24 hrs	4ml/kg/hr
Second 10 kg	50ml/kg/24 hrs	2ml/kg/hr
Each subsequent 1 kg	20ml/kg/24 hrs	1ml/kg/hr

e.g. 24kg: = (100x10kg) + (50x10kg) + (20x4kg) OR 4x10kg) + (2x10kg) + (1x 4kg)
= 1000 + 500 + 80 = 40 + 20 + 4
= 1580ml per 24 hours = 64ml per hour x 24
= 1536ml per 24 hours

This shows that either method of calculating fluids is acceptable, giving reasonably close answers for fluids for a 24 kg child over a 24-hour period (indeed, the difference between the 2 methods is less than 2ml/hr).

In addition to the above maintenance fluid requirements, *on-going losses* (e.g. due to significant gastrointestinal losses i.e. diarrhoea or vomiting, polyuria) need to be considered and replaced.
In ***febrile*** patients, *insensible losses through sweating and respiration will be higher than usual;* add +/- 13% extra fluid for each 1 degree C > 37.5 degrees C.

Replacement Fluid (Deficit = existing + on-going losses)

On-going losses, e.g. due to significant diarrhoea or vomiting, may be replaced intravenously on a ml-for-ml basis or as part-replacement if the patient is also tolerating some oral fluids. In practice, this involves adding up the previous 4-6 hours losses and replacing them intravenously, either as a short infusion, or over the subsequent 4-6 hours.

Existing losses (i.e. dehydration)

Percentage dehydration can be estimated clinically using the following parameters:
(APLS guidelines)

To calculate Replacement fluids (according to % dehydration):

Fluid deficit (ml) = Percentage dehydration x Weight (kg) x 10

Resuscitation fluids

In an acutely unwell / dehydrated or shocked child, resuscitative fluids may be urgently required. Recommendations according to APLS guidelines are to give 20ml/kg of isotonic (0.9%) saline as an initial bolus, and then reassess according to usual clinical criteria. A second 20ml/kg may be given if required, **but the need for this should raise the alert that anaesthetic and senior assistance /assessment is required as a matter of urgency.** (See separate guidelines on 'Shock')

e.g. A 24 kg child is 7.5% dehydrated, calculate fluid requirement.
(Assuming no resuscitation required)

Fluid deficit = 7.5 x 24 x 10
= 1800ml
(OR 7.5/100 x 24 x 1000)

Maintenance = (100 x 10kg) + (50x 10kg) + (20x 4kg)
= 1000 + 500 + 80
=1580ml

Thus Total fluid requirement = Maintenance + Deficit + Resuscitation fluids
= 1580ml + 1800ml + 0
= 3380ml over 24 hours
(+ addition for on-going losses on a ml-for-ml basis)

Electrolyte levels must be considered when considering choice of fluid & speed of rehydration. In a patient with hypernatraemic dehydration (Na>145), rehydration must be slow, i.e. over 48 hours rather than 24 hours. In hyponatraemic or normonatraemic dehydration, rehydration should be over a 24-hour period. (See section on hyper- and hyponatraemia.)

Choice of Fluids

1. Maintenance fluids & replacement of existing deficit

The majority of children may safely receive sodium chloride 0.45% with glucose 5% or sodium chloride 0.45% with glucose 2.5% (both hypotonic solutions). There is currently little evidence to recommend a particular strength of glucose.

Sodium chloride 0.45% with glucose 2.5% (+ 20mmol KCl per litre of fluid) is normally used as hydration fluids with chemotherapy. Some regimens specify the addition of magnesium.

Sodium chloride 0.45% with glucose 2.5% (NO POTASSIUM) is normally used in the prevention and management of tumour lysis).

0.18% NaCl with 4% glucose should be restricted to use in PICU or in a renal unit.

Some children at high risk of hyponatraemia should preferably receive isotonic solutions (sodium chloride 0.9% with glucose 5%, sodium chloride 0.9% or compound sodium lactate solution (Hartmann's solution)

- intravascular volume depletion / hypotension ;
  sepsis ;
- excessive gastric or diarrhoeal losses;
- central nervous system (CNS) infection;
- head injury;
- bronchiolitis;
- salt-wasting syndromes;
- chronic conditions such as diabetes, cystic fibrosis and pituitary deficits.

It is important to monitor electrolytes levels and adjust potassium concentration of fluids accordingly. Urine dipstick should be done routinely to monitor for hyperglycaemia.

2. Replacement fluids – on-going losses

Choice of replacement fluids for on-going losses should mirror the fluid being lost, with attention to electrolyte levels. Usually, losses due to diarrhoea or vomiting may be replaced using 0.9 % saline with added potassium (usually 20mmol KCl per litre of normal saline, but adjust according to electrolytes)

3. Resuscitation Fluids

There has been much debate over the years as to whether the resuscitation fluid chosen should be crystalloid, colloid or a combination of both. Current APLS guidelines recommend an initial 20ml/kg bolus of a crystalloid with electrolyte concentrations mirroring those of serum, i.e. 0.9% saline or Hartmann's solution. If response is inadequate, a 2nd 20ml/kg bolus of the same fluid should be given.

Features of Commonly used Intravenous Fluids in the UK[1]

	Osmolarity (mOsmol/L)	Sodium content mequiv/L)	Osmolality (compared to plasma)	Tonicity (with reference to cell membrane)
Sodium chloride 0.9% with glucose 5%	586	150	Hyperosmolar	Isotonic
Sodium chloride 0.9%	308	154	Isomolar	Isotonic
Sodium chloride 0.45% with glucose 5%	432	75	Hyperosmolar	Hypotonic
Glucose 5%	278	-	Isomolar	Hypotonic
Glucose 10%	555	-	Hyperosmolar	Hypotonic
Hartmann's *	278	131	Isomolar	Isotonic
Sodium chloride 0.18% with glucose 4%	284	31	Isomolar	Hypotonic
Sodium chloride 0.45% with glucose 2.5%	293	75	Isomolar	Hypotonic
4.5% human albumin solution	275	100-160	Isomolar	Isotonic

Weinberg et al (2016) Plasma-Lyte 148: A clinical review[12]

Table 1 Characteristics of common crystalloid solutions compared to human plasma

	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Acetate (mmol/L)	Gluconate (mmol/L)	Lactate (mmol/L)	Malate (mmol/L)	eSID (mEq/L)	Theoretical osmolarity (mOsmol/kg)	Actual or measured [1]osmolality (mOsmol/kg)	pH
Plasma	136-145	3.5-5.0	0.8-1.0	2.2-2.6	98-106	Nil	Nil	Nil	Nil	42	291	287	7.35-7.45
Sodium chloride (0.9%)	154	Nil	Nil	Nil	154	Nil	Nil	Nil	Nil	0	308	286	4.5-7
Compound sodium Lactate (lactate buffered)	129	5	Nil	2	109	Nil	Nil	29	Nil	29	28	278	5-7
Ringer's lactate (lactate buffered)	130	4	Nil	3	109	Nil	Nil	28	Nil	27	278	256	5-7
Ionosteril® (acetate buffered solution)	137	4	1.25	1.65	110	36.8	Nil	Nil	Nil	36.8	291	20	6.9-7.9
Sterofundin ISO® (acetate and malate buffered)	145	4	1	2.5	127	24	Nil	Nil	5	25.5	309	Not stated	5.1-5.9
Plasma-Lyte 148® (acetate and gluconate buffered)	140	5	1.5	Nil	98-106	27	23	Nil	Nil	50	295	271[2]	7.4[3]

[1]Freezing point depression; [2]Australian and New Zealand formulation; however approximate osmolality may vary depending on country of manufacture; [3]Australian and New Zealand formulation; however pH ranges from 6.5 to 8.0 depending on country of manufacture. Plasma-Lyte 148 manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ringer's Lactate manufactured by Baxter Healthcare, Deerfield, IL, United States; Hartmann's solution manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ionosteril manufactured by Fresenius Medical Care, Schweinfurt, Germany; Sterofundin ISO manufactured by B. Braun Melsungen AG, Melsungen, Germany.

Electrolyte concentrations - intravenous fluids[5]

- ***Compound Sodium Lactate (Hartmann's)***

Sodium	131 mmol/litre
Potassium	5 mmol/litre
Bicarbonate	29 mmol/litre
Chloride	111 mmol/litre
Calcium	2 mmol/litre

- ***Sodium Chloride 0.18% and Glucose 4%***

Sodium	30 mmol/litre
Chloride	30 mmol/litre

- ***Sodium Chloride 0.45% and Glucose 5%***

Sodium	75 mmol/litre
Chloride	75 mmol/litre

- ***Potassium Chloride 0.15% and Glucose 5%***

Potassium	20 mmol/litre
Chloride	20 mmol/litre

- ***Potassium Chloride 0.15% and Sodium Chloride 0.9%***

Sodium	150 mmol/litre
Potassium	20 mmol/litre
Chloride	170 mmol/litre

Electrolyte content - gastro-intestinal secretions[5]

- ***Gastric***

Hydrogen	40–60 mmol/litre
Sodium	20–80 mmol/litre
Potassium	5–20 mmol/litre
Chloride	100–150 mmol/litre

- ***Biliary***

Sodium	120–140 mmol/litre
Potassium	5–15 mmol/litre
Bicarbonate	30–50 mmol/litre
Chloride	80–120 mmol/litre

- ***Pancreatic***

Sodium	120–140 mmol/litre
Potassium	5–15 mmol/litre
Bicarbonate	70–110 mmol/litre
Chloride	40–80 mmol/litre

- ***Small bowel***

Sodium	120–140 mmol/litre
Potassium	5–15 mmol/litre
Bicarbonate	20–40 mmol/litre
Chloride	90–130 mmol/litre

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14.

MANAGEMENT OF LATE EFFECTS IN SURVIVORS OF CHILDHOOD CANCER

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14. Management of Late Effects in Survivors of Childhood Cancer

Gonadotoxicity, Fertility Impairment and Fertility Preservation

Endocrinopathies, including fertility problems, are among the most prevalent late effects of childhood cancer treatment. Rates of fertility impairment are 42-66% among male and 11-26% among female CCS, with higher rates among those who received alkylating agents and/or pelvic radiation. ALL survivors treated on older protocols (1962-79) experienced more late effects involving reproductive system than those treated more recently (1991-2007). Gonadal damage in children and AYAs treated for cancer can result from either systemic chemotherapy or radiotherapy delivered to the gonads. Among chemotherapeutic agents, alkylating agents in particular can impair fertility and the risk increases with cumulative doses, as estimated by the cyclophosphamide equivalent dose (CED).

Males

The agents commonly used in haematological paediatric malignancies that are most often associated with oligo/azoospermia in males include cyclophosphamide, ifosfamide, busulfan and melphalan. Although there is individual variation in risk of gonadotoxicity after exposure to alkylating agents, the cumulative dose likely to produce azoospermia has been established for most agents. Cumulative doses of cyclophosphamide >5-7.5 g/m^2 are associated with abnormal semen parameters, and azoospermia was consistently observed after total cyclophosphamide dose >19 g/m^2, ifosfamide >60 g/m^2 (CED=>15 g/m^2), busulfan >600 mg/m^2 (CED>5.3 g/m^2) and melphalan >140 mg/m^2 (CED>5.600 mg/m^2). Combinations of alkylating agents have an additive effect on gonadotoxicity. In males, impaired spermatogenesis was unlikely when CED was ≤4 m/m^2. Prepubertal status at diagnosis is not protective against alkylating agent germ cell toxicity in males. Alkylating agent-associated azoospermia is usually permanent although recovery of normal spermatogenesis years after treatment has been described.
The testicular germinal epithelium is particularly sensitive to radiotherapy. Testicular doses as low as 0.1 Gy impair spermatogenesis, and recovery is unlikely after a single testicular dose exceeding 4-6 Gy. Treatment with imatinib in chronic myeloid leukaemia showed no significant association with low testosterone concentration. Testicular Leyding cells responsible for steroidogenesis are more resistant to radiotherapy and chemotherapy then Sertoli cells involved in spermatogenesis. Testosterone production is often maintained wait CED ≤ 20 g/m2, however subclinical damage of Leyding cells may follow. Steroidogenesis is compromised in prepubertal males receiving testicular radiation of > 20 Gy while > 30 Gy induces the same effect in older boys. Subclinical dysfunction of steroidogenesis may occur with lower doses of testicular radiotherapy of 12 Gy. In HSCT CCS treated without radiotherapy, the occurrence of delayed puberty is uncommon.

Females

Females are born with a fixed number of ovarian primordial follicles, which varies between individuals and declines with age. Radiotherapy at an older age is associated with greater dose-related risk, as the result of a smaller oocyte pool at the time of treatment. Doses of 5 Gy can impair ovarian function in post-pubertal girls (10 Gy in prepubertal), and doses ≥10 Gy (≥ 15 Gy in prepubertal age) are considered as higher risk for gonadal failure. According to the rate of oocyte decline, mathematical modelling suggests that the sterilizing dose is 20.3 Gy in infants, 18.4 Gy at age 10 years, and 16.5 Gy at age 20 years. Doses as low as 2 Gy have been estimated to deplete a follicular pool by as much as 50%. The risk of radiotherapy is

increased by addition of alkylating chemotherapy. TBI is a major risk factor of premature ovarian insufficiency (POI).
Alkylating agent-induced ovarian failure directly correlates with cumulative dose and age at exposure. Survivors who received CED at or above 6-8 g/m^2 are considered to be at high risk of POI. Non TBI HSCT survivors who received busulfan as conditioning regimen were at a greater risk for ovarian failure compared to those conditioned with cyclophosphamide, treosulfan, thiotepa or melfalan (68% vs 29%). Survivors of a reduced-intensity HSCT conditioning regimen comprising fludarabine and melphalan, compared to a myeloablative regimen comprising busulfan and cyclophosphamide, took significantly longer to develop ovarian insufficiency from the onset of puberty. Methotrexate and vinca alkaloids have minimal or no gonadotoxic effects.
Combinations of drugs with low or moderate gonadotoxicity may cause severe ovarian damage, hence busulfan (16 mg/kg – CED 4.24 g/m^2) with low or high doses of cyclophosphamide (120 or 200 mg/kg; CED = 3.6 or 6 g/m^2) caused permanent ovarian damage to almost all patients.
CRT doses causing lower pregnancy rates varied significantly by study, but even low doses (18-24 Gy), as used in historical ALL protocols, have been reported to decrease fertility rates compared with sibling controls. Doses >30 Gy demonstrated the highest risk for fertility impairment.
Most AML survivors treated with chemotherapy only had normal pubertal development and fertility. However, anti-Mullerian hormone (AMH) levels were decreased in 13% of post-pubertal females, implying a potential risk of POI in female AML survivors.

Fertility preservation options:

International bodies recommend discussing the impact of gonadotoxic therapy on future fertility and fertility preservation (FP) options—strategies implemented in an attempt to retain fertility opportunity when it is threatened by gonadotoxic therapy—at the timely manner .
However, time constraints, the anxiety and vulnerability of the patient and the volume of information relayed, as well as potentially limited clinician knowledge regarding FP or lack of FP Service, can impair the provision of fertility-related information .
Furthermore, whilst oocyte or sperm salvage have proven efficacy, procedures for pre-pubertal children (ovarian or testicular tissue cryopreservation) are considered experimental —although recent advances may mean this will change rapidly—adding to the complexity of the decision process and the potential for long-term regret around a decision made prior to exposure to gonadotoxic treatment.
Decision regret (distress or remorse) about healthcare decisions negatively impacts the wellbeing and quality of life of patients . High levels of decision regret have been associated with poorer long-term health outcomes, poorer psychological wellbeing and an overall lower quality of life . Decisions regarding FP have the potential to create high levels of long-term regret. Studies on adult female cancer survivors have demonstrated high regret that can be lessened with pre gonadotoxic treatment counselling and thus supports the clinical recommendations for pre-treatment FP discussion.
However, there is minimal published literature evaluating decision regret regarding FP decisions in paediatric and adolescent populations . Paediatric fertility preservation creates a unique situation whereby future cancer survivors and their parents (acting as surrogate decision-makers) could both experience regret. The additional anxiety and responsibility of having to make a decision that is inconsistent with the child's future preferences may increase their risk . Understanding of the experiences of regret support clinical recommendations and need for solid FP Service for pre pubertal children exposed to fertility damaging therapy.

Please refer to CCLG Oncofertility document :
https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/CCLG_Oncofertility_Final_Oct2019.pdf

Late effects in Survivors of Childhood Cancer

In the UK over 1700 children under the age of 15 years are diagnosed with cancer every year. Survival statistics have highlighted that, at present, over 75% of patients can be expected to be long term survivors. The Pan-Thames London childhood cancer population is served by three principal treatment centres (PTC) and a large number of POSCUs across North and South Thames regions. The present estimate is that over 1800 long term follow-up patients are actively seen in the London area. There are a greater number of patients not actively seen, but who may require surveillance.

Long term sequelae can present at the end of treatment but, more importantly, can occur several years later. As a part of the NHS Cancer Reform Strategy the **National Cancer Survivorship Initiative** was set up in 2008. It outlines a 5-year plan to improve patients' experience of living with cancer and beyond. The vision sets out that all cancer survivors should have:

-Individualised assessment and care plan
-Support to self-manage their condition
-Information on the long-term effects of living with and beyond cancer
-Access to specialist medical care for complications that occur after cancer treatment

In order to translate this into clinical practice, current management (where possible) should reflect the following pathway:

1. Referral of the survivor to the Late Effects clinic in a PTC, is usually 5 years after completion of treatment, but in certain circumstances (ie post HSCT or following brain tumour treatment) it may be earlier.

Referral criteria for Specialised Endocrinology Late Effects clinics:

a) Children who have received haematopoietic stem cell transplantation (autografts or allografts) for a primary haematological and/or oncological diagnosis
b) Children who have received Radiotherapy as bone marrow transplant conditioning e.g. TBI /cranio-spinal boost or haemato-oncology chemotherapy treatment protocols i.e. CNS radiotherapy, localized radiotherapy
c) Children who have received chemotherapy treatment protocols known to lead to endocrine sequelae i.e. pubertal/fertility/linear growth/thyroid dysfunction

Note: Referrals for children with suspected endocrine dysfunction not included in any of the above categories will be re-directed to a routine outpatient endocrinology service.

Referrals for children with reproductive medicine issues pre haematopoietic stem cell transplant will be directed to University College Hospital, Endocrinology or Gynaecology services as appropriate.

Age /Timing of Referral, for children who satisfy above referral criteria:

a. Age at referral for boys 12 years
b. Age at referral for girls 11 years
c. Irrespective of age, all children who have received TBI/Craniospinal boost based bone marrow transplant conditioning protocols should be referred to HAEGRO at two years post HSCT for baseline growth assessment and formal growth hormone testing, when appropriate.

d. Children who have shown evidence of linear growth failure in the haematopoietic stem cell transplant late effects follow up clinic

2. At referral, a multi-disciplinary meeting (Late effects clinician, endocrinologist, specialist nurse, psychologist and social worker) is held to devise a future plan for follow-up.

3. An individualized Care Plan is drawn up (*Appendix A*) which includes treatment summary, clinical systems at risk and outlines surveillance guidelines (*Appendix B*) for late effects, based on therapy received.

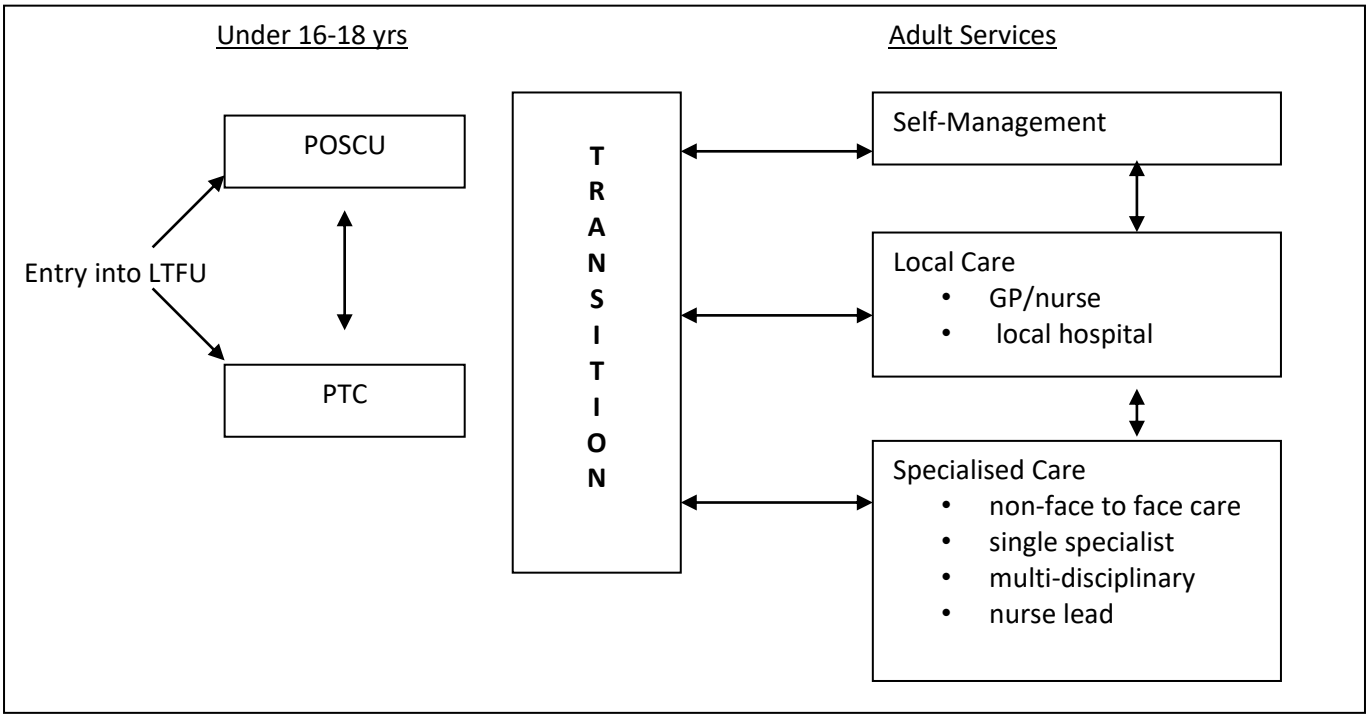
4. Either based on the individualized Care Plan or a Level of Care (*Appendix C*) assigned to a patient; follow-up may be in the PTC or shared with the POSCUs. The long-term objective is to develop a cost-effective service which is patient centred, locally based where possible, age appropriate and takes into account the individuals' risk of developing late consequences of treatment.

5. If the child is being followed-up in a local POSCU, then at 16 yrs (or in some cases 17-18 years), of age they should return to the Late Effects clinic at the PTC or to the adult long term follow-up clinic at 18 years of age if available locally (e.g in Brighton).

6. Following this, the goal is to prepare patients for transfer to the adult clinic which is done between the ages of 18-24 years depending on local set-up. Gradually, as services get better organised, level 1 and 2 patients will be discharged into primary care for managed self-care. However, provision should be made for surveillance investigations to take place in a timely manner and the PTC database updated annually. If the patient develops problems, they should be able to return to the teenage or adult clinic for review as required.

It must be recognised that the pathway outlined below is dependent on local services and resources.

Patient Pathway



Aims of long-term follow-up

1. The timely diagnosis and treatment of late toxicities which may include:

    a. Cardiovascular, neurocognitive, neurological, psychological, audiological, skeletal, dental, metabolic and endocrine late effects.
    b. Prevention by identifying and treating pre-symptomatic hormonal abnormalities (growth, pubertal delay or advancement, thyroid or parathyroid over or under activity and cortical deficiency)

2. To provide information to survivors about future late effects eg. CCLG AfterCure booklets (www.aftercure.org), fact sheets and local information sheets.
https://www.cclg.org.uk/Publications/late-effect-factsheets
3. To advise on lifestyle and health education issues, such as smoking and exposure to UV light

4. To discuss job selection, insurance etc.

5. Research: The survivors of childhood cancer provide an extremely important cohort for research into the incidence, natural history of late effects and the effect of treatment intervention. This research then influences the development of new protocols, and provides valuable information for the survivors, newly diagnosed patients and their families.

Survivors of childhood cancer at follow-up should have an opportunity to discuss the following

1. Quality of Life: Relationships, emotional function and sexual function, concerns re physical appearance and function, work performance including employment, insurance and related issues.

2. Compliance with medications, e.g. anti-infective prophylaxis, anti-hypertensives, hormone replacement therapy.

3. Lifestyle choices: smoking, alcohol and other risk behaviour

4. Exercise, diet and bone health

5. School attendance and performance

For the survivor and his/her family, this addresses their primary area of concern and also helps the clinician identify services for additional support in the school or local community.

Below is a brief tabulated summary of clinical history, examination and surveillance investigations which should be considered in long term survivors of childhood cancer. Surveillance is therapy based and individualized Care Plans will highlight specific late effects. Investigations may be carried out locally, based on resources.

Table 14.1 Summary of clinical history, examination and surveillance investigations

Surveillance in clinic	Late Effects to consider	Tests	Advice/Referral
Height, Weight, BMI	Obesity	Fasting glucose, lipids, LFT Assess insulin resistance/glucose tolerance if severe	Dietary advice (low GI diet) graded exercise
Height velocity, sitting height, pubertal stage	Early or late puberty, growth hormone deficiency	Gonadotrophins, sex hormones, thyroid function, bone age	Refer to Late Effects-endocrinology service
Menstrual history, erectile dysfunction, Tanner stage	Gonadal /germ cell failure or Leydig cell dysfunction	Gonadotrophins, sex hormones, thyroid function. Semen analysis when appropriate	Refer to Late Effects-endocrinology Assisted reproduction service
Joint pain (hip, knee) gait, fractures	Osteopenia/osteoporosis/ Avascular necrosis	Bone profile, DEXA scan/MRI	Encourage a calcium-rich diet, exercise. Refer to Late Effects-endocrinology service
Hearing and speech development	Sensori-neural hearing loss	Audiological tests	Refer to Audiology/speech and language therapist
Vision	Cataracts, dry eyes	Ophthalmoscopy	Refer to Ophthalmology
Dental Health	Caries, short dental roots, microdontia	Dental and oral mucosa examination	Advice on dental hygiene and refer to dentist/specialist orthodontist
Skin	Naevi, basal cell carcinoma in irradiation field	Measure number, change in size, pigmentation, surface	Refer to Dermatology
Exercise tolerance, shortness of breath	Cardiac dysfunction or obstructive/restrictive pulmonary defect	ECHO/ECG and/or pulmonary function tests	Refer to Late Effects-cardiology service
Renal	Isolated hypertension, glomerular/tubular dysfunction	Blood pressure, U&E, urinalysis for proteinuria and haematuria. Estimate GFR if appropriate	Refer to Late effects-renal service
New masses, regular breast examination, neck masses, brain tumours	Second malignant neoplasms	Imaging	Refer to Late Effects-biopsy and further management

NB This not an exhaustive list but an illustration of common problems

All long-term survivors should have an identified key worker for clinicians/families to contact with concerns.

At Great Ormond Street Hospital the Long Term Follow Up administrator has been identified as a Keyworker and can be contacted on 0207 813 8127 or ltfu@gosh.nhs.uk. Concerns will then be forwarded to the relevant clinicians. At RMH the key worker who is a clinical nurse specialist can be contacted on 0208-661-3329. The key worker for the TYA service can be contacted on 0208-661-1238. At UCLH referrals are either directly to the lead clinician Dr Victoria Grandage (Victoria.grandage@nhs.net), or Lead Nurse Susan Mehta (susan.mehta@nhs.net) or via the late effects coordinator ucl-tr.LateEffectServ@nhs.net. The service at UCLH is predominantly for adolescent, young adult and adult survivors of childhood cancer.

Chapter 14 - Appendix A

Individualised Care Plan

(This document may be modified in the future)

Treatment Summary and Long Term Follow Up Plan

Name:		**Hosp/NHS No:**	/
Date of birth:		**Sex:**	
Address:		**Consultant:**	

Diagnosis		**Diagnosis Date:**	
Stage/Group:		**Treatment End Date:**	
Trial/Protocol:			

Recurrence of Disease No

Date	Site/s	Management Summary
	Select	

Chemotherapy Yes

Drug Effects to Monitor	Dose
Select	
Select	
Select	

Surgery Yes

Date	Details

Radiotherapy No

Date	Site/s	Total Dose	Fractions	Normal Tissues within Field	Notes
	Select	Gy		/ /	
	Select	Gy		/ /	

Bone-marrow transplantation/PBSC No

Type	Select	**Date**	
Conditioning Regimen			
Drug Effects to Monitor		**Dose**	
Total Body Irradiation		***No***	

Complications during treatment No

Complications after treatment Yes

Other Studies N0

Familial factors and syndromes N0

Treatment summary completed by:

Print Name Date / /2010

Print Title Clinical Nurse Specialist

Systems at Risk and Care Plan

Growth Problems: Should be none.

Growth hormone started	**Select**	**Start Date**		**Finish date**	
Final height (cm)		cm	**Date**		
Onset of Puberty					
Other growth problems		**Select**			

Fertility Problems: Select Discussion with patient
Select **Date**

Menarche Date			
Regular Periods?	**Select**	**Date**	
Semen analysis Result		**Date**	

Hormone Problems: Should be none.

Heart Problems: Should be none.

Pre-treatment Result	Echo		**Date**	
Post-treatment Result	Echo		**Date**	
Follow-up Result	Echo		**Date**	
Follow-up Result **Blood Pressure Result**	Select mmHg		**Date**	
Other abnormalities	/			

Lung Problems: Should be none.

Pre-treatment Result	Select		**Date**	
Post treatment Result	Select		**Date**	

Kidney Problems: Should be none.

Pre-treatment GFR Result	Select	mL/min	**Date**	
Post treatment GFR Result	Select	mL/min	**Date**	

Follow Up GFR Result	Select	mL/min	**Date**	
Renal tubular dysfunction	Select	mL/min	**Date**	

Problems with Brain/Nerves: Should be none.

Problems with other Organs/Tissues: Should be none.

Organ/Tissue	Details
Audiology	

Psychosocial/school/occupation issues

Lifestyle

It is important to maintain a healthy lifestyle with a balanced diet, including '5 a day' of fruit and vegetables and taking part in regular exercise. Additionally avoid smoking and limit alcohol intake.

Offspring (live births and miscarriages)

Information given to Patient/Family

Information	*Date given*
select /	
select /	
select /	

Follow-Up Plan

☐ **Disease Related Follow Up at**
☐ **Disease Related Follow Up at shared care hospital - Select**

☐ **Long Term Follow Up at PTC**
☐ **Long Term Follow Up at shared care hospital - Select**
☐ **Long Term Follow Up with GP**

Long Term Follow Up due: Select Year.
Frequency of Long Term Follow Up, every: Select Frequency.
Review of follow-up plan
Name of shared care Consultant: _____

Surveillance Required

	Investigation	*Start Date*	*Frequency*
	GENERAL		Every appointment
☒	Height and weight		
☒	Pubertal status		
☒	Blood pressure		
☐	Urinalysis		
	BLOOD TESTS		
☐	Full blood count		
☐	Urea & Electrolytes (Kidney Function)		
☐	Liver Function Test		
☐	Lipid profile (Cholesterol etc.)		
☐	Glucose		
☐	Anterior Pituitary function tests		
☐	Gonadotrophins (Sex Hormones)		
☐	Thyroid Function		
☐	GFR (Kidney Function)		
☐	Others		
	OTHER		
☐	Chest x-ray		
☐	DEXA Bone Scan		
☐	Interval MRI scan		
☒	CT Scan		
☐	Echocardiogram (Heart Function)		
☐	ECG (Heart Function)		
☐	Lung Function Tests		
☐	Audiometry (Hearing Test)		

Long Term Follow Up Care Plan completed by:
Print Name **Date**
Print Title **Clinical Nurse Specialist**
Confirmed by MDT **Date**

References

Therapy based guidelines are web based, readily accessible and easy to use in clinic, if further guidance is needed.

www.ukccsg.org.uk/public/followup/PracticeStatement/index.html

Therapy based long term follow up: Practice Statement. UK Children's Cancer Study Group

www.survivorshipguidelines.org

Children's Oncology Group: Long-Term follow-up guidelines for survivors of childhood, adolescent and young adult cancers

www.Sign.ac.uk/pdf/sign76.pdf

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15.

SOCIAL AND FINANCIAL SUPPORT AVAILABLE TO FAMILIES

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15. Social and Financial Support Available to Families

The experience of coping with a diagnosis of childhood cancer is probably one of the most distressing life events that a family can face. All families with a child undergoing treatment for malignant disease are likely to need considerable emotional and practical support.

As treatment progresses many families become increasingly aware of the impact of the illness on their sick child, healthy siblings, as well as the marital and wider family relationships. Family members may welcome the opportunity to talk about their fears and feelings or seek information about how to access support for themselves, possibly through a parent support group. Apart from the emotional trauma of the illness the practical and financial impact can pose a serious strain on family functioning. Families frequently incur extra expenses travelling to and from treatment centres. In addition they may incur extra costs on heating, diet, childcare expenses, telephone, clothing etc. Frequently the disruption caused by the illness and treatment may hinder parents' ability to work and this can have an adverse effect upon family finances.

Supporting patients and families

In 2005 Nice published guidance on how the NHS in England should deliver services to children and young people with cancer. The aim of this guidance was to improve not just clinical outcomes but the holistic experience of care for children and their carers. As a consequence of this guidance a review was set up and led by CLIC Sargent with the aim of developing a model of care which would best meet needs both in hospital and in the community. The key messages from this review "More Than My Illness" are as follows:

- Ensuring children and young people have access to information and are empowered to make informed choices
- The importance of the Key worker role as care co-ordinator
- Assessment and care planning processes at key stages of the treatment pathway
- Tailoring packages of care that are unique to a child and their family and take account of clinical, educational, social, emotional, practical and financial needs

Assessment of a child and family's psychosocial needs is not a static event, but something that needs to be constantly revisited at key stages of the treatment pathway. Key trigger points for reassessment of a child or family's needs following initial medical diagnosis might be:

- Any changes of concern in the child's health and general development, behaviour or mood
- Any changes of concern in a parent or care giver (as above)
- Any changes in a parent or care givers personal circumstances
- Impact of environmental factors such as housing, finance, employment, schooling etc
- Transitions – i.e. end of treatment, referral to long term effects clinic, transfer to adult care
- Relapse
- Palliative care

Bereavement

Accessing help

The charity, Young Lives vs Cancer, funds specialist social work posts in all principal treatment centres across the UK and in some shared care hospitals. Young Lives vs Cancer social workers provide a service to children and young people under the age of 25 years affected by any form of cancer or who are undergoing cancer-like treatment. These social workers are able to offer an assessment of a child and family's emotional, social and practical needs. On-going support is offered on an individual, family or group basis, including end of life and bereavement support.

Accessing additional financial support to manage the extra costs of care is a major concern for most families. Young Live vs Cancer social workers have a good knowledge of statutory and voluntary support services available, as well as grant making agencies, and can ensure that families access financial and other practical support appropriately. This includes linking in with a dedicated Welfare Advice Line to provide advice across a range of areas including benefits, housing, employment etc and how to access these resources.

Young Lives vs Cancer also recognises the emotional impact a diagnosis can have, and the Social Workers are there to talk through this with children, young people and their families.

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Alternatively, advice about benefits can be obtained from the local citizens advice bureau.

Further details about the services and support offered by Young Lives vs Cancer, and other useful information can be found on www.younglivesvscancer.org.uk

Referrals to Young Lives vs Cancer are usually undertaken through the local MDT of the hospital where the child is being treated. However, a referral or self-referral can also be made by:
Tel: 0300 303 5220 / Email: getsupport@younglivesvscancer.org.uk
Search Young Lives vs Cancer and use Live Chat on our website

Financial Assistance

Welfare reform

The benefits system is in the process of major change. The Welfare Reform Act 2012 has introduced a variety of changes to the benefit and tax credit systems. Some have taken effect; others will be rolled out over the next few years.

One of the main changes is the introduction of a benefit called Universal Credit which will replace six income related benefits namely:

- Income support
- Housing benefit
- Child tax Credit
- Working Tax Credit
- Income related Employment and Support Allowance
- Income Based Job seekers Allowance

The benefits listed above will be phased out between October 2013 and 2017. By 2017 the Universal Credit system will be fully operational. Families in receipt of the six benefits named above will be contacted over a period of time to arrange transfer to Universal Credits.

Whilst it is not possible here to list all available state benefits the main benefits that families should consider in relation to a malignant diagnosis are:

Disability Living Allowance (DLA) for Children

This benefit is for children under 16 years who have a serious illness or disability that need more help and assistance than other children of a similar age. Normally this help must have been needed for at least **3 months** and must be likely to be needed for at least a further **6 months**.

Disability Living Allowance has two parts called 'components':

- a care component - if you need help looking after yourself or supervision to keep you safe
- a mobility component - if you are unable to walk or find it very hard to walk, or you need help getting around

Some people will be entitled to receive just one component; others may get both.
The care component and mobility component are paid at different rates depending on how their disability affects them
.
DLA is not payable as of right. It is assessed on "need for care" after completion of a detailed form, part of which also has to be signed by someone who knows the child well, i.e. a carer, doctor, social worker, etc.

Personal independence Payment

Personal Independence Payment (PIP) is a new benefit that helps with some of the extra costs caused by long-term ill-health or a disability for people aged **16 to 64**.

To qualify a person must have a long-term health condition or disability and have difficulties with activities related to 'daily living' and or mobility. They must have had these difficulties for **3 months** and expect them to last for at least **9 months**.

Claims for PIP will be assessed by an independent health professional to help DWP work out the level of help needed. This may be a face-to-face consultation.

DWP makes the decision about the claim based on the results of the assessment, the application form and any supporting evidence included.

Special rules for Disability Living Allowance/PIP

If it is deemed that a child/young person's life expectancy may be less than 6 months – it is possible to get these allowances processed more speedily and ensure that the care component of the benefit is paid at the highest rate. To get an application considered under the "special rules" it is necessary for a doctor to complete a DS1500 medical form for inclusion with the application.

Being in receipt of Disability Living Allowance/PIP may increase the number of other benefits or credits individuals are entitled to such as:

- Income Support
- Income-related Employment and Support Allowance
- Income-based Jobseeker's Allowance

- Pension Credit
- Housing Benefit
- Council Tax Benefit
- Working Tax Credit
- Child Tax Credit

N.B. note that some of these benefits will in time be replaced by Universal Credit

Disability Living Allowance/PIP is normally ignored as income for working out these income-related benefits and credits.

Carers Allowance (CA)

One parent/carer can apply for CA. The benefit is:

- Payable to a person caring for a sick or disabled child, who is in receipt of DLA care component at the middle or higher rate or PIP Personal Independence Payment daily living component
- Payable if the parent/carer does not earn above a certain amount
- This benefit is treated as income.

Further information about benefits is available from The Department of Work and Pensions (ww.dwp.gov.uk) or local Citizens Advice Bureau. The latter organisation is particularly helpful for families who are dealing with debt and money management problems that require more specialist input.

Debt management

Families of a child undergoing cancer treatment may be more likely to get into debt due to reduced income and higher outgoings associated with treatment costs. However it may be that they were managing significant debt prior to diagnosis which will have the effect of increasing overall stress levels.

Debt management is a complex topic and families should be encouraged to seek help as soon as possible. The CLIC Sargent welfare advice service and the Macmillan Cancer Support website can provide practical support and advice about how to approach this issue. Alternatively any local CAB office can put families in touch with accredited money advice services.

Other Organisations offering support:

Useful contacts:

1. Macmillan Cancer Support

89 Albert Embankment
London SE1 7UQ
Tel 0808 808 0000
Email cancerline@macmillan.org.uk
Web site www.macmillan.org.uk

A national charity providing expert treatment and care through specialist Macmillan nurses and doctors. Macmillan also provides grants for patients 18 years and above, experiencing financial difficulty.

Macmillan Benefits Advice

Tel- 0800 808 0000

This service checks people's entitlement to benefits and will offer assistance with forms. Is also able to offer advice about employment and debt

2. Childhood Cancer Parent Alliance CCPA (formerly NACCPO)
CCPA
Rachel Olley
Operations Manager
SDVS, 131-141 North Walls
Stafford. ST16 3AD
Web site www.naccpo.org.uk
Tel/Fax 01785 603763
Email ro@naccpo.org.uk

CCPO is an umbrella organisation for parent run groups in the UK. It is a national voice for parents and families, working with the Government, the CCLG Young Lives vs Cancer and other bodies on such issues as education, job security and shared care treatment.

3. Children's Cancer Recovery Fund

71-75 Shelton Street
London, WC2H 9JQ
Tel 0207 470 8755
www.cancerecovery.org.uk

Provides a fund for emergency payments of utility bills, rent payments, council tax, travels costs, TV licence. Maximum grant £300

4. Kids Cancer Charity – (formerly Christian Lewis)

62 Walter Road
Swansea, SA1 4PT
Tel 01792 480500

Fax: 01792 480700
Web site www.kidscancercharity.org

Offers financial grants, crisis break holidays in the UK and an information and advice service to families. They can also assist with organising travel insurance and can help to co-ordinate cost effective all-inclusive travel packages for Euro Disney and Disney World Florida

5. Leukaemia Care Society

One Birch Court
Black Pole East
Worcester WR3 8SG
Tel 01905 755977
Email care@leukaemiacare.org.uk.
Web site www.leukaemiacare.org.uk

A national group promoting the welfare of people suffering from leukaemia allied blood disorders. It offers limited financial assistance, travel insurance, support and regional support groups. In addition caravans are available for members' holidays in the UK.

6. Lennox Children's Cancer Fund

Suite D, 7-11 High Street
Romford, Essex RM1 1JU

Tel: 01708 734366
Fax: 01708 749421
Web site www.lennoxccf.org.uk

Provides financial assistance and holiday provision.

7. Lymphoma Association

PO Box 386
Aylesbury
Buckinghamshire
HP20 2GA
Tel 0808 808 5555
Fax 0808 808 5555
Email support@lymphomas.org.uk
Web site www.lymphomas.org.uk

Provides information and emotional support to anyone whose life is affected by Lymphoma. The helpline is staffed by people who have knowledge and understanding of the treatment of Lymphomas. Produces information leaflets

8 . Together for Short Lives
4th Floor, Bridge House,
48-52 Baldwin Street,
Bristol, BS1 1QB
0117 989 7820

National Helpline: 0845 108 2201

This is an umbrella organisation, which is working to improve the standard of care and support, which should be universally available throughout the UK for children with life threatening conditions and their families and professionals, though not specifically focused on malignancy.

9. Action for Sick Children

Action for Sick Children
32b Buxton Road
High Lane
Stockport SK6 8BH
Tel 01663 763004
Helpline 0800 0744519
Web site – www.actionforsickchildren.org

The aim is to ensure sick children obtain the highest standards of care in hospital, at home and in the community.

10 . Contact a Family

Contact a Family
209-211 City Road
London EC1V 1JN
Tel 020 7608 8700
Fax: 020 7608 8701
Helpline 0808 808 3555 or Textphone 0808 808 3556 Free phone for parents and families (Mon-Fri, 10am-4pm; Mon, 5.30-7.30pm)
Web site www.cafamily.org.uk

Helping families who care for children with any disability or special needs via telephone help line, local support groups and publications

11. Disability Rights UK

12 City Forum
250 City Road
London EC1 8AF
Tel 020-7250 3222.
Fax 020 7250 0212
Web site www.radar.org.uk

E-mail: enquiries@disabilityrightsuk.org

National organisation run by and working with disabled people. Gives information and advice on all issues relating to disability. Produces a wide range of publications and fact packs on disability issues

12. Rainbow Trust Children's Charity

Rainbow Trust Children's Charity
6 Cleeve Court
Cleeve Road
Leatherhead
Surrey KT22 7UD

Tel 01372 363438
Web site www.rainbowtrust.org.ukFamily centred care for children with life threatening illnesses. They offer family support services within the home

13. REACT (Rapid Effective Assistance for Children with Potentially Terminal Illness)

React
St Luke's House
270 Sandycombe Road
Kew, Richmond
Surrey, TW9 3NP
Tel 020 8940 2575
Fax 020 8940 2050
Web site www.reactcharity.org

Supports families through making financial grants or purchasing equipment to facilitate their care at home. Provides holidays for families.

14. SIBLINKS

1 Betjemin Close
Coulsdon,
CR5 2LU
Web site www.siblinks.org.uk

SIBLINKS is a national initiative aimed at providing web-based help and support to older siblings (15-25) of children or young people with cancer.

15. The Family Fund

4 Alpha Court
Monks Cross Drive
York. YO32 9WN
Email info@familyfund.org.uk
Tel 08449 744 099*
Text phone 01904 658085
Fax 01904 652625
Web site www.familyfund.org.uk

Their purpose is to ease the stress on families who care for a very severely disabled child under 16, by providing grants and information relating to the care of the child

16. The Youth Cancer Trust

5 Studland Road
Alum Chine
Bournemouth BH4 8HZ
Tel 01202 763591
Fax 01202 769064
Website www.youthcancertrust.org.uk
Aims to provide holiday breaks for young people aged 14-25 with cancer, who can also be accompanied by a sibling or friend.

17. UK Brain Tumour Society

Brain Tumour UK
Tower House
Latimer Park
Chesham HP5 1TU
Helpline 0845 4500 386
Admin tel 01494 549 180
Email enquiries@braintumouruk.org.uk
Website www.braintumouruk.org.uk

Provides information and support for anyone affected by the diagnosis of a brain tumour.

18. Wessex Cancer Trust

Bellis House
11 Westwood Road
Southampton
Hants SO17 1DL
Tel 0238067 2200
Fax 0238067 2266
Counselling service 0238067 2255
Email wct@wessexcancer.org**Back to Contents**
Web site www.wessexcancer.org

A regional cancer charity which raises funds to complement and initiate improvement of cancer care services in Wessex. Services include free counselling, befriending, complimentary therapy services, information leaflets, financial assistance and holiday provision.

Useful Publications

Better care: better lives – improving outcomes and experiences for children, young people and their families coping with life limiting and life-threatening conditions - **DOH 2008**

More than My illness – delivering quality cares for children with cancer - **CLIC Sargent 2009**

The Impact of Cancer on a Child's World - - the views of children aged 7-13 living with and beyond cancer – **CLIC Sargent 2010**

More than my illness: delivering quality care for young people with cancer – **CLIC Sargent 2010**