PALLIATIVE MEDICINE

PAIN AND SYMPTOM CONTROL IN THE CANCER AND/OR AIDS PATIENT IN UGANDA AND OTHER AFRICAN COUNTRIES

A pocket book for health professionals

Fifth Edition

Prof. Dr Anne Merriman, Hospice Africa (Uganda)

Dr Eddie Mwebesa, Hospice Africa (Uganda)

Prof. Elly Katabira, Hospice Africa (Uganda)

In 2009, HAU was recognised by the National Council of Higher Learning as the Institute for Hospice and Palliative care in Africa (IHPCA).

The new logo incorporates the institute which cannot exist without the clinical support of patients, from whom we learn so much.

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FOREWORD BY THE HONOURABLE MINISTER OF HEALTH

I am indeed delighted to write the foreword to the fifth edition of this very popular book known colloquially as the 'Blue Book".

We in the Ministry of Health have now incorporated palliative care into our Health Sector Strategic Plans since 2000. Palliative care has advanced so much since the fourth edition of this book was produced in 2006. Palliative care was already acknowledged as an essential clinical service under HIV/AIDS for all Ugandans. This year, emphasis is for palliative care to be extended to Non Communicable Diseases (NCDs). This is due to the growing need in all countries, but especially in Africa today. The Ugandan Palliative Care Country team has, since 2002, been working on increasing the prescribers for oral morphine throughout Uganda. *Uganda became the first country in the world in 2003 to change the Government statute allowing midwives to prescribe pethidine for women in labour, to nurses and clinical officers who have undergone a 9 month registered training at a recognised specialist institution to prescribe morphine for their patients.* This was in line with the WHO recommendations of 1996[1] and

1 WHO (1996) Cancer Pain Relief

more recently in their recommending of "task shifting" to bring such services closer to the people.

From 2004, the Ministry of Health has provided oral morphine free throughout the 54 districts at that time, where training has been carried out for health professionals in palliative care including pain control. Meanwhile the Ministry of Health has also given scholarships to allow selected nurses and clinical officers from several districts to have the training to enable them to prescribe morphine and to pass on their skills to health professionals and community volunteers in the villages. In 2012 a rapid prescriber's course of 6 weeks, for upgrading clinical officers to be prescribes of oral morphine, has commenced and is increasing prescribers more rapidly. These too will be registered as prescribers. Our Ministry is dedicated in releasing these specialist nurses and clinical offices (DCPCs and Rapid Prescribers) to be free from other duties and to work in their districts for palliative care needs. These trained personnel are nourished by the Palliative Care Association of Uganda with regular updates. With the formation of district branches of PCAU, they can meet and discuss difficult cases and get support from other Hospice and palliative care specialists, now available in Uganda.

The commonest patients needing palliative care are those with critical or end of life conditions due to HIV/AIDS and cancer. It is estimated that 30% to 80% of patients with AIDS have pain. Fifty five out of the 112

districts in Uganda now have been trained and have access to oral morphine. However more than 50% of people in Uganda do not access a health professional in their life time, and these too die of cancer, HIV/AIDS and other NCDs. Thus it is important to have community selected volunteers, trained to work as vigilantes to detect those suffering and trained to care so they can give initial care in the home and alert palliative care teams to visit their homes and relieve pain and symptoms. This is now happening in many parts of Uganda. Palliative care teams are also working closely with traditional healers, who are the first contact for many suffering patient and families. Working with them we can use affordable medications for symptoms from tried and tested traditional and conventional medicines.

Services for definitive treatment of HIV/AIDS have increased in the last few years with the introduction of the PEPFAR and Global Fund initiatives for HIV/AIDS, TB and malaria. This has led to some free and more reduced prices on imported and generic antiretroviral drugs. However for the majority of patients with HIV/AIDS and cancer, palliative care still remains the only hope and humanitarian relief. The major challenges to the provision of palliative care services are inadequate number of palliative care practitioners and weak regulatory mechanisms reducing the availability and accessibility of relevant drugs at community level. These needs were recognised in 2003 and are being met through

my Ministry by ensuring suitable procurement, distribution, storage, prescription and use of drugs according to international and national regulations. The Ministry of Health has addressed these challenges by training more health workers in palliative care, availing drugs and issuing guidelines for handling of class A drugs. Review of the laws governing classified drugs have been written from the procurer to the patient including delivery of class A drugs in the home.[2]

Palliative care training was introduced into the medical schools at Makerere University in 1993 and in Mbarara University of Science and Technology in 1998. These two medical schools have produced doctors and nurses well versed in the new specialty and some more senior doctors are opting for the specialty. However as new medical schools are opening there is a great need for specialists to teach in these new Universities and inspire the doctors of the future to bring such care to their patients. Palliative care is now in the curricula of most other training institutions. This is in line with the WHO objective of freedom from cancer pain being a right of every patient. It is therefore important to build on what Hospice Uganda initiated in 1993 and now widely adopted by the Ministry of Health, NGOs and health training institutions.

This fifth edition will be important in highlighting the issues of pain management.

2 Ministry of Health, Uganda (2001): Guidelines for Class A Drugs

It is intended for those working with HIV/AIDS and/or cancer in Uganda and Africa. The remedies used are those that are affordable and can be made available by Ministries of Health in Africa. It has also presented new advances in palliative care including the management of those on ARVs and the diagnosis of those who will require ARVs. Here in Uganda there is a close networking system with those institutions giving ARVs and those dealing with families. There are referrals to these organisations and referrals back to Hospice for palliative care. The "Blue Book" fifth edition will go a long way in assisting health workers to provide quality services to patients. This book is in demand both in Uganda and the rest of Africa due to its unique African approach to the economic and culturally acceptable remedies enabling the patient and family to come to peace with professional support during critical illness and at the special time coming to the end of life.

For the sake of all the patients who need pain and symptom relief during their last days and the health workers who take care of them, I am very pleased to write this foreword.

Hon. Dr. Ondoa J. D. Christine,
Minister of Health,
Uganda.
22nd June 2012.

PREFACE TO FIFTH EDITION

Welcome to the fifth edition of the "Blue Book". This edition is again dedicated to all those who are caring anywhere in the African Continent, with dedication, to bring relief of suffering and peace to their patients and families. HIV is declining in some African countries but in South Africa and countries adjacent, it is still a major problem. This year the AIDS section has been edited by Professor Dr Elly Katabira, who is probably the most experienced doctor in HIV/AIDS in Africa to date.

Since the last edition, through advocacy, oral morphine solution, the most affordable and suitable analgesic for severe pain, has become available in more countries in sub Saharan Africa. One of the main problems at the moment is to prevent the "stock outs" of morphine solution, which throw our patients back into unbearable suffering. Kenya and Nigeria have now taken a major step forward with the appointment of a National Fellow by GAPRI (Global Access to Pain Relief Initiative). The main purpose is to ensure someone will check all the many bureaucratic blocks that can happen, when advocacy has not been brought to those handling the documentation necessary in country to ensure smooth and regular importation of the powder and sufficient manufacture and access within the country. Some countries are making up their morphine solution in a central place but others are making it up in pharmacies nearer to patients. This is particularly important in a large country like Nigeria, where with 160

Million inhabitants; morphine production needs to be available not only in the country but in every geo political zone (GPZ) and within the GPZ, every state. Hospital palliative care teams are not effective unless linked with home care teams which can ensure pain control and holistic palliative care in the community through to the end of life. Thus it is most important that the formula is available everywhere and the Blue Book is bringing this to all. Also because of the increased movement between countries in Africa, it is essential that we keep the solutions safe by colour coding which is recognised across borders. You will read in the appendices on formulae, the colour coding commenced in Uganda and which is now moving through Africa. With green for 5mgs per 5 ml., red for 50mgs per 5 ml., and blue for 100mgs per 5 ml. The price to give complete pain control for the average patient consuming 30 mgs per day, is now the price of one and a half loaves of bread , which is double that of 6 years ago.

Of course the coordination of pain control and the provision of supportive palliative care is essential. Palliative care Associations in country and with branches according to the size of the country and the population, have a huge responsibility in keeping an up to date register of the sites where palliative care can be received. As more prescribers become available, more patients' will receive this form of care. This is achieved through the specialised training of Initiators and

prescribers, as well as through higher education with Bachelors and Masters degrees now available in a few countries in Africa.

Noerine Keleeba, the founder of TASO, Uganda, in her book "We Miss You All", describes the suffering of her husband while ill with cryptococcal meningitis in 1986:

"He was in great pain. I can't even begin to describe the kind of pain he was in. He had this terrible headache which lasted for five days. He never lost consciousness. He suffered all that pain and we felt the pain with him. The children would come into the room and he would ask for a wet towel to be put around his head. Even today, my baby Christine, who was barely three at the time, remembers Daddy's headache and if anyone says that they have a headache Christine becomes very anxious. If I have a headache I don't always tell her because she has very bad memories of that headache."

We, who introduced palliative medicine and oral morphine to Uganda in 1993 and have now treated more than 20,000 patients without diversion or addiction, want to share through this book, our experiences in bringing peace to patients and families.

The Distance Learning Diploma in Palliative care for Africa has been upgraded to a degree. Those with the former Diploma or with the Diploma in Clinical Palliative care can now enter the degree programme at second year. Although accredited by Makerere University,

the degree is created and delivered at the Institute of Hospice and Palliative Care in Africa (IHPCA), at HAU in Kampala. The first degree class graduate in January 2013. There are now approximately 30 students per year and this is really increasing the capacity of clinical care and education programmes throughout sub Saharan Africa. We hope that we have lit "fire in the belly" and that this will light flames as you carry your candle within your own countries. Thus you will bring service and training to your people.

This book is a result of our work and experience over 20 years with palliative medicine in Uganda. The original edition, which was written in the UK by Dr. Derek Doyle and Dr. TF Benton from St. Columba's Hospice in Edinburgh, continues to be expanded as we gain more experience with cancer and AIDS patients and families in Uganda and other African countries.

This fifth edition has an updated section on antiretroviral drugs, their management, effect on disease and ethical issues in the African situation. This section was originally contributed by Dr Karen Frame, MRCP. Karen is now a Consultant in palliative care in London. She is teaching palliative care at both Schools of Tropical Medicine in London and Liverpool and is the lead person for our UK link called the "Shoestring". She has widespread experience in palliative care and HIV/AIDS in Uganda. We are most grateful to her.

There is a definite link between cancer and AIDS. However the increase in cancer is now also associated with an increasing life expectancy. In Uganda in 1993 life expectancy was 38, it is now 54 and increasing. Although Kaposi's sarcoma (epidemic), non Hodgkin's lymphomas and other AIDS defining cancers are still present, there has been a huge increase in women's cancers including cervix, breast and ovary. More recently there has been a huge increase in men of cancer of the oesophagus, which has even exceeded cancer of the prostate and is of course more fulminating. Unfortunately the statistics only include those who are diagnosed in hospitals and this is only a fraction of the sufferers. Many stay at home seeking help elsewhere and we do not hear of them. Fifty seven percent of Ugandans do not reach a health worker and we are now focusing reaching this section of the population who are the poorest and have many unmet needs at this time of life, by working with Community Volunteer workers. These workers are selected by their communities and given special training in caring for and identifying those in need of palliative care. Many who never reach a Health Professional are in need and only through these special CVWs can they be reached. As a result the major source of our referrals to HAU have changed from hospital referrals to self or community volunteer referrals, and for many, we are the first health workers they have ever seen.

Since the fourth edition published in 2006,

there have been many achievements in palliative care services in Uganda and these are mentioned in the Foreword by the Minister of Health. There has also been greater access to anti retroviral treatments. Some patients are now presenting for critical or end of life care, that have been on ARVs, presenting with different symptoms and with side effects of the ARVs as their renal function changes coming towards the end of life. Others on ARV's, who seem to be doing very well, must feel free to receive palliative care when dealing with symptoms from side effects or intercurrent infections. The palliative care worker must be aware of the drugs being used and their metabolism and side effects and cost. We have therefore updated the section on ARV's by Dr Karen Frame. An earlier section looks at ethical issues surrounding withdrawal of ARVs in a resource strapped society.

Every village and every family in Uganda has experienced the death of a loved one from AIDS. Many of these patients have died at home. Many have also had cancer. The AIDS support teams are increasingly becoming trained in palliative care. However as long as donors respond to numbers rather than quality of care, palliative care will not be part of a full programme for those support organisations dependent on funding from such donors. Palliative care is time intensive and when time is not there, then palliative care is not being given with the sensitivity and meaning required at this special time of life.

Hospice Africa Uganda introduced palliative care and the modern methods of pain and symptom control which are now working so well in the home. The training of personnel in this specialty is a major part of the work of Hospice Uganda. Since 2000, when palliative care was included for the first time as an Essential Clinical Service for all Ugandans, in the Strategic health Plan 2000-2005, (and emphasised in subsequent strategic documents) we are working ever more closely with the Ministry of Health, Kitovu Home Care, IDI, TASO and Mildmay, and other networking organisations. This is also coordinated through the Palliative Care Association of Uganda (PCAU) which continues to hold CME on a quarterly basis while following up all those trained and delivering palliative care throughout Uganda. PCAU was the first such organisation in Sub Saharan Africa and is itself a model for other countries.

The Ministry of Health has made oral liquid morphine available to those Districts who have been sensitised to the guidelines for class A drugs and the health professionals trained in the diagnosis and management of pain. This is free of charge to the patient. Since 2011, the morphine for all Uganda is being produced at HAU in Kampala. It is just manageable for our relatively lower population of 34 Million but the population is growing rapidly and we need to look to the future.

Every health professional has a responsibility to teach where they work in countries with

so few health professionals. Our training programmes bring training methods to those on the courses so that they in turn can train health and non-health professionals alike. Those from other African countries are taking these concepts with them on their return. Families and the community manage so well when they have the support of an approachable team. It is hoped that those who use this book will be able to take a special form of care to their own family and village.

The Hospice Ethos[3] for African Hospices and palliative care services is an essential part of our training and based on three elements:

1. The patient and family are at the centre of all that we do

2. We support each other in our own teams so that we feel supported and able to bring this support to all in need.

3. That we recognise and support our networking organisations, recognising that none of us alone can reach all in need in Africa today.

This book is to complement our courses and to assist those in hospitals and the community who have not had the opportunity to attend them. As more and more health professionals learn the principles of palliative care, Governments in African countries are aiming at making medications available throughout

3 Ethos for Hospices in Africa: available from the website *www.hospiceafricauganda.or.ug*

each country, but this is a "push and pull" system. You the health professionals need to provide the "push" and demonstrate the needs of the suffering. Only those medications available in Uganda at the time of writing are mentioned in this book. Those who wish to seek the use of other medications are referred to the recommended further reading books given from each section and in the references at the end of the book.

The sections referring to the management of the AIDS patient are the result of our experience and that of the expert doctors who are dealing every day with the AIDS patients. We are most grateful to them for allowing us to share in clinics and for their sharing their expertise with us when teaching on our courses.

The principles of palliative care are applicable to all patients who are dying from whatever cause. The student in palliative care will have gained skills which will be useful to him/her throughout their professional lives. It is hoped that this book will be useful, not only in Uganda, but in all other African countries faced with similar problems.

Anne Merriman
30 June 2012

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My deep gratitude goes to the following:

- Dr. Derek Doyle, for allowing the re-editing of his book "Palliative Medicine, Pain and Symptom Control" 1991 edition, for the needs of Uganda.
- Dr Robert Twycross for permission to adapt his body charts for appendix 1, and his always being available for advice.
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- The Hospice Team in Makindye, Kampala, Mobile Hospice Mbarara and Little Hospice Hoima, who have supported the identification of affordable and acceptable treatments for the patients and families, and for the love and care they give to each other. They also continue to contribute cultural insights so that we can serve our patients better.
- The patients and families who have welcomed us into their homes and hearts, while showing us a special kind of Ugandan caring.

- The Minister of Health, Honourable Christine, for the encouragement and support that she has given to the spread of palliative care throughout the country. To all the previous Ministers of Health who, by promoting the use of morphine and other medications in the Districts, and for support in adapting a statute so that palliative care nurse and clinical officer specialists can now prescribe morphine, have brought comfort to many.
- Dr. Jacinto, Amandua, Commissioner for Clinical services at the Uganda Ministry of Health, for always being available to support the promotion of relief for the suffering in Uganda.
- To our donors who have made this work possible and have contributed to the publications of Hospice Uganda, particularly SCIAF, Scotland and Diana, Princess of Wales Memorial Fund, London, USAID and DFID through the THET grant.
- To those health professionals in African countries who have embraced the Hospice Philosophy thus changing medicine in its entirety to that of hospitality more than bureaucracy.
- Most of all we are grateful to God for enabling this work to spread throughout Uganda and to other African countries and for his deep compassion for those suffering and their families.

Professor Dr Anne Merriman, June 2012
Hospice Africa Uganda

INTRODUCTION

This book is for the use of Doctors, Clinical Officers, Nurses and Pharmacists in Uganda and other African countries. Only those medicines and methods of pain control available in Uganda in this year of 2012 are discussed. For a wider knowledge of medications available elsewhere see recommended reading below, particularly PCF4 (Palliative Care Formulary 2012, Twycross and Wilcox).

The reader is reminded that the principles of pain and symptom control, discussed in this book, are applicable to all chronic or incurable diseases, especially in the terminal stages. The philosophy of caring and being there for every development of the illness with love and scientific expertise to alleviate suffering and support families will help health professionals in their daily patient encounters.

To understand the course of diseases that we are writing for in particular, we have shown in graphic form the Clinical course of AIDS and of cancer (figures 1 & 2). However whatever the course of the disease, palliative care including the holistic approach to pain and symptom control should be available at any stage of both diseases as well as other life limiting illnesses.

- The control of pain was the essential component of the holistic approach that was missing in Uganda and the other African countries that we have been

visiting since 1990. Support care was already there in many areas for patients in the home. However the support falls short when pain cannot be controlled during critical illness and at the end of life. Even the most highly trained counsellor is left inadequate in the face of the unrelieved terrible suffering of cancer and/or AIDS. The management of pain and symptoms is indeed the most important aspect of care and this should be available to all and in the place most suitable to them, usually the home.

- Home care without the team having the knowledge or the medications for pain and symptom control is support care only and cannot be called palliative care. However this book together with training programmes now becoming available throughout Uganda and reaching to other African countries is one of the essential tools for making pain and symptom control a reality for already existing home care support teams such as TASO in Uganda and other similar organisations throughout Africa.

- Persuading Governments to make effective, affordable drugs for palliation available is sometimes difficult but with good advocacy this may not be very difficult as it has been observed in the various countries we have visited. There are so many other priorities in

developing countries. However we cannot minimise the need to advocate for affordable palliative care, which fulfils the human right of all patients to be free from pain. Anti-retroviral agents (ARVs) although not universally accessible are now more available, because of support from many donors. Patient numbers on ARVs are growing rapidly. 57% of our people in Uganda never see a health worker. They too have cancer and/ or AIDS. Throughout Africa countries, Palliative care must be prepared to have a public health approach, reaching the poorest by identifying them first with a situational analysis of their needs followed by a service designed to meet those needs.

- Morphine is now the cheapest analgesic available in Africa when it is made up in the country from powder which costs today, 9 UgSh or 0.4 US cents per mg and the price of a loaf and a half of bread, which can leave most patients pain free for 2 weeks. In Uganda we are privileged to have the Government paying for this so it is free to all those who are in pain when prescribed by a recognised prescriber. Other countries are still turning patients away who cannot pay and this is so sad.

- Those promoting palliative care services must keep an eye on the local prices of other medications on the essential drug list for palliative care (Page 244).

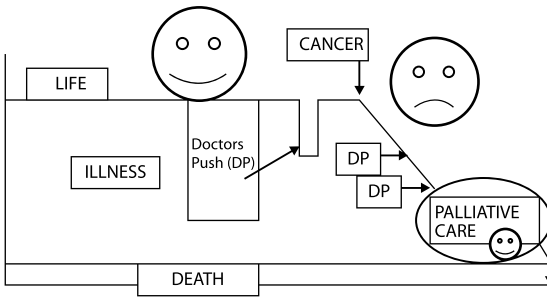
Prices vary from country to country. The generic drugs are always cheaper than the brand named drugs and are equally effective.

- This book is also aimed at all those who care for their brothers and sisters and want to give them love and care, including pain and symptom control, in that very special time before death, when secrets can be shared and families can come close.

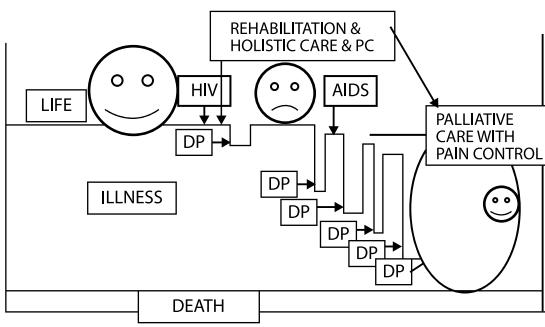
The most important tools for the clinician (doctor, clinical officer or nurse) in palliative medicine are:

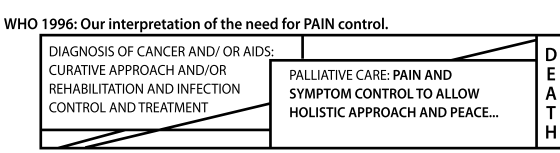
- time
- a case record adapted to local circumstances, accurately documented
- medications available and affordable
- clinical skills and the patience to apply holistic knowledge to bring peace and comfort to the patient and family

CANCER:



HIV/AIDS





Adapted from WHO 1996:

Figure 1: Graphic representation of the cancer journey versus the HIV/AIDS journey and implications for intervention and approach using palliative care.

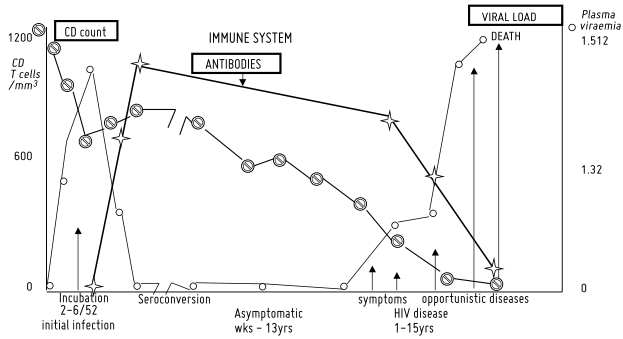


Figure 2: Progress of HIV disease

THE HOLISTIC APPROACH

"Holistic" means that the patient is viewed as a person with physical, psychological, social, spiritual and cultural gifts and needs which are special to that person. Each of these aspects must be taken into account. These items of information can be captured in a holistic case record (see appendix 7) .The patient is seen in the context of his/her family and local community, so that family and community are involved in caring and the health worker carries on caring into bereavement for the family. "Holistic" also means that the team takes a holistic approach, using the different talents in a team to assist in various aspects of the illness. In Africa there is frequently a paucity of rehabilitation staff such as physiotherapists, occupational therapists, counsellors and social workers.

It must be noted that 57% of people in Uganda and 85% of people in Ethiopia, do

not access a health worker in their lives! This figure is even higher in some other African countries. A palliative care team often consists of a Nurse alone. We have the added responsibility of training and using family members and local volunteers, giving simple basic nursing skills and showing them how to identify pain and symptoms. This training in different methods of assistance must include counselling and supporting families.

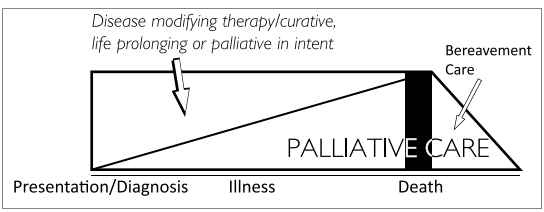
APPROACH TO THE CANCER PATIENT VERSUS THE AIDS PATIENT

Throughout this book we will try to enable readers to change their approach from the curing to the palliative mode while dealing with the dying patient. Palliative care is not an alternative to other models of health care. It is not in competition with efforts to provide antiretroviral and other advanced therapies, nor is it a poor relative to be implemented where such therapies are currently inaccessible. It is an essential part of a comprehensive health care system, which is missing in many developing countries, and must not be neglected in efforts to provide greater accessibility to more technical drugs and therapies.

Palliative care should be an integral part of the comprehensive care and support for people living with HIV/AIDS and cancer patients. It should be provided as a continuum of care from the time of diagnosis of any of these incurable diseases until the end of life. It should not be looked at as only care at

the time of death. Palliative care, including symptom management should be applied as early as possible in the course of the cancer and/or HIV/AIDS trajectory. The patient and family need not go through unnecessary suffering as we wait for laboratory results and 'curative' treatments.

However there is a difference in approach to the AIDS patient compared to the cancer patient, depending on the stage of the illness.



Adapted from: American Medical Association. Institute for Medical Ethics (1999) *EPEC: education for physicians on end-of-life care.* Chicago, Ill: American Medical Association: EPEC Project, The Robert Wood Johnson Foundation.

Figure 3 Continuum of Care

CANCER

In Uganda and other African countries, a cure in cancer is quite rare due to the cost and paucity of investigations and curative treatments i.e. surgery, chemotherapy and radiotherapy. Also most patients present too late or the therapy is not available at the right stage of the disease. It is estimated that less than 5% of cancer patients in developing countries have access to these forms of treatment.

Palliative care can be introduced to the cancer patient at any stage of the illness, particularly when pain and distressing symptoms are present. In the occasional patient who presents very early in the illness, intercurrent infections or surgical complications should be treated aggressively.

The majority of patients presenting to Hospice Uganda sadly are in a debilitated state. Here the role of the palliative care team is to ensure patient comfort and to protect them from unnecessary and/or expensive investigations and aggressive interventions such as ventilation, which are not now going to be of any benefit. If cancer patients are close to death, IV fluids are rarely helpful and may in some instances increase discomfort, due to fluid overload, contributing to overload of the circulation, heart failure and oedema of the skin.

It is vitally important that relatives understand that such interventions will not benefit the patient, so that they can be re-assured that all reasonable efforts have been made by them and that the goals of care have now become a peaceful dignified death.

The health worker gains experience in judging the stage of the disease only by caring for many patients.

AIDS

The patient with AIDS often presents with opportunistic infections which may or may

not be terminal. Many of these opportunistic infections can now be prevented – primary and/or secondary prophylaxis – using co-trimoxazole and fluconazole (for cryptococcal meningitis). These medications, previously inaccessible, are now being funded from Governments through donors.

The aim of treatment is to allow this patient to recover from each opportunistic infection so that he/she can regain a normal life and perhaps live for many more months or years. Thus the patient presenting with severe diarrhoea needs to be given supportive management (rehydration with i.v and oral fluids) that will allow him to return to the family as a breadwinner. In contrast, such an episode of diarrhoea in a cancer patient may be due to the cancer itself. Having been with the patient for some time, the team is in an admirable position to judge the stage of the illness. However, if the patient is unknown to the team and presents with severe dehydration, an aggressive approach using i.v fluids would be correct if the history was not available. Often by taking an accurate history and discussing with the patient and family, the stage of the disease can be gauged.

AIDS TO DIAGNOSIS AND PROGNOSIS IN HIV/AIDS:

Patients may present without a laboratory confirmation of their HIV status and many patients in Africa still do not have access to such facilities even though the situation has tremendously improved in the last five years.

Many cancer patients also have HIV/AIDS. It is therefore useful to know of indicators, which can suggest not only the presence of the virus and therefore prompt referral to HIV testing facilities, but also the clinical stage of the disease and therefore the prognosis. (see WHO staging below).

DISCERNMENT

As explained above, discernment of the stage of the disease only comes with experience. So how does a new palliative care team manage? It is important that the clinical leader of the team is approachable and able to discuss the indications for management having taken into account the stage of the disease and the clinical state of the patient. The team should be able to come together and discuss the pros and cons of active versus palliative management for each individual patient and be able to explain why or why not any course of action has been implemented.

DIAGNOSIS

Suspect in a patient with two or more of the following:

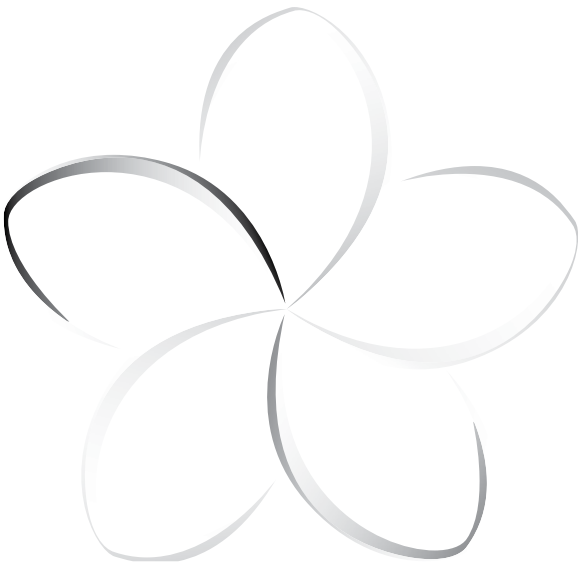
▪ Kaposi's Sarcoma ▪ Cryptococcal meningitis ▪ Oesophageal candidiasis or ulceration ▪ Herpes Zoster if under 50 years of age ▪ Oral thrush under 50 years of age unless with a known other cause of immuno-suppression or diabetes.	▪ Severe skin rash ▪ Recurrent fevers for >month ▪ Recurrent diarrhoea >a month ▪ Persistent generalised lymphadenopathy (PGL) especially in children ▪ History of high risk behaviour – multiple sexual partners, Intrvenous drug abuse (not a common mode of transmission in Africa), etc. ▪ Spouse or partner died of HIV – related complications. ▪ History of blood transfusion after 1975

WHO STAGE: CLINICAL SYMPTOMS WEIGHT LOSS PERFORMANCE SCALE

WHO STAGE:	CLINICAL SYMPTOMS	WEIGHT LOSS	PERFORMANCE SCALE	
WHO STAGE 1	Nil or PGL (persistent generalised, lymphadenopathy)	Nil or slight	1	Normal
WHO STAGE 2	Minor skin rash Herpes Zoster Recurrent URTIs Recurrent oral ulcers	<10%	2	Normal
WHO STAGE 3	History of more than one month of: Chronic diarrhoea or Recurrent fevers Oral thrush Pulmonary TB in last 2 years, Severe presumed bacterial infections	>10%	3	In bed < 50% of time over last month
WHO STAGE 4	Cryptococcal meningitis, Toxoplasmosis of the brain, Kaposi's sarcoma, Dementia, HIV wasting, Pneumocystis carini pneumonia, Oesophagial candidiasis, Extrapulmonary TB, Recurrent bacterial pneumonia, Chronic herpes simplex infection	++++	4	In bed >50% of time over last month

The above information can be plotted against figure 2 (page 6) and give an idea of the patients stage and prognosis. Diagnoses of many of the illnesses in the WHO staging can be made clinically or with cheap/ available investigations.

SECTION I:
THE CONTROL OF PAIN



This flower represents the simple affordable measures that can be used to control pain in Africa. These include the sap of the frani pangi. This flowering bush is available in all countries in Africa and application to the lesions of herpes Zoster, can relieve the dreaded neuropathic pain

SECTION I: THE CONTROL OF PAIN

1.1 Definition of pain:

The international association for the study of pain (IASP)[4] defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain is subjective; individuals create their own definition of pain based on their experience. Thus, pain is whatever the experiencing person says it is, existing whenever the experiencing person says it does. "Pain is what the patient says hurts."

Pain is the commonest symptom experienced by the dying and certainly the most feared. It is present in 98% of patients referred to Hospice Uganda with cancer and/or HIV/AIDS. Various studies all over the world, have demonstrated an unacceptably high proportion of patients dying with poorly controlled pain. This is widely the case in Africa. The reasons for this include:

Not giving enough time to the patient and not listening to what they are saying or implying.

- Waiting for the patient to complain of pain and expecting him to describe it in the more helpful detail usually met in acute conditions. The more advanced a chronic illness, the less

4 IASP website *www.iasp-**pain**.org*: accessed 18 May 2012

is reported and the more vague the description. "Pain not reported" does not mean "pain not present".

- Failure to realise that 60% of patients have more than one pain.
- Failure of the doctor to elicit details of pain from attending nurses and relatives who usually know the patient better than the doctor does.
- Lack of knowledge in diagnosing and managing different pains in cancer and/or AIDS patients.
- Prescribing the right drug in the wrong dose, or with the wrong frequency.
- Omitting an appropriate adjuvant (drugs marketed for other indications than pain but in certain circumstances control pain[5]).
- Fear of opioids causing the death of the patient.
- Withholding strong opioids because of the misplaced fear of addiction or respiratory depression.
- Failure to consider the use of other methods of pain control if available, e.g. surgery, radiotherapy, hormones or cytotoxic chemotherapy.
- Failure to regularly and frequently review the patient's pattern of suffering and the regimen being used.
- Failure to take into account the complex emotional, social, cultural and spiritual factors present in every dying patient.

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5 Palliative Care Formulary (PCF4) *www.palliativedrugs.com*

1.2 PAIN IN CANCER VS PAIN IN AIDS:

It must be remembered that the analgesic ladder and treatment of pain was originally conceived for cancer pain. Cancer pain is usually constant and increases with progression of the disease. In developing countries where less that 5% of cancer patients have access to chemotherapy or radiotherapy, the natural history of pain is that it is progressive up to the time of death.

In an African study of patients with stage IV AIDS, the commonest pains were:

Lower limb pain (66%) (due to peripheral neuropathy)

Mouth pain (50.5%)

Headache (42.3%)

Throat pain (39.8%)

Chest pain (17.5%)

Many of these pains occur due to opportunistic infection and are therefore sometimes transient in nature e.g. oro-pharyngeal pain due to candidiasis. This is particularly true in the earlier stages of the illness. In these situations it is often necessary to use strong analgesia e.g. morphine, for the duration of the painful episode, and then to withdraw the analgesia gradually once infection/cause has been treated and pain has resolved.

1.3 THE PRINCIPLES OF PAIN CONTROL

When diagnosing pain, there are therapeutic implications. Pain can be divided into two physiological entities, nociceptive and neuropathic.

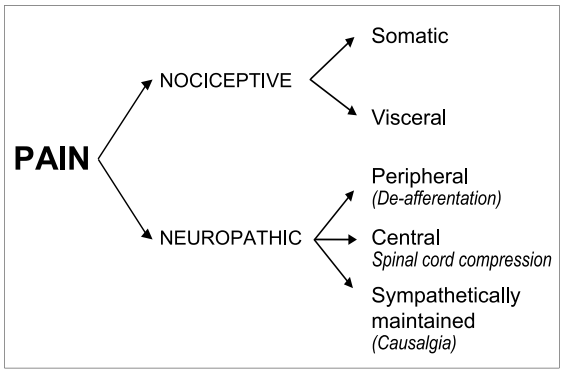
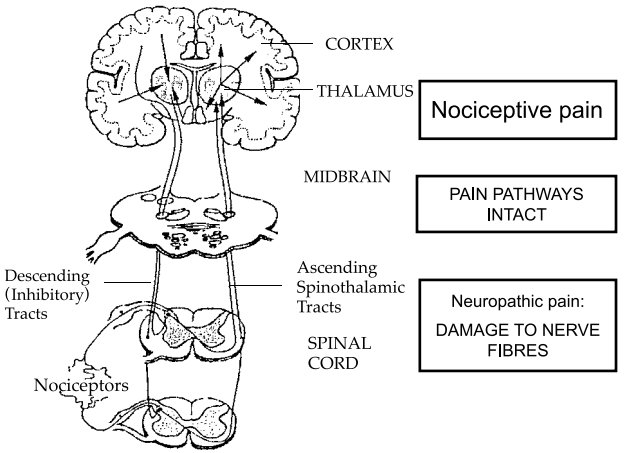


Figure 4: Classification of pain

1.4 NOCICEPTIVE AND NEUROPATHIC PAIN

This distinction is useful as nociceptive/ normal pain tends to respond well to standard medication using WHO ladder, whereas neuropathic/nerve pain may need the addition of extra "adjuvant" medication e.g. tricyclic antidepressants.



A. Nociceptive "Normal" Pain:

The perception of nociceptive input described in terms of tissue damage. It indicates that the nerve pathways are intact, i.e. the feeling of pain is a normal response to a noxious stimulus e.g. pain from a fractured bone, aching muscle etc. Nociceptive pain is subdivided into somatic and visceral pain. Somatic pain arises from damage to body tissues and it is usually well localized. Visceral pain on the other hand, is pain arising from the viscera mediated by stretch receptors. It is poorly localized, deep, dull, and cramping (e.g., the pain of appendicitis, cholecystitis and pleurisy).

Nociceptive pain usually responds well to the drugs of the WHO analgesic ladder. (see below).

B. **Neuropathic pain:**

The term "neuropathic"/nerve pain refers to pain caused by damage to the peripheral or central nervous system. It may remain persistent even without ongoing disease (e.g., diabetic neuropathy, trigeminal neuralgia, or post herpetic neuralgia). When a nerve becomes damaged, changes within the neural pathways can result in chronic pain even in the absence of a continuing stimulus.

It indicates that there is damage to the nerve pathways. Neuropathic pain may not respond as well to the drugs of the analgesic ladder alone, but usually requires additional "adjuvant" medications as well as standard WHO ladder.

Ninety-eight percent of patients referred to Hospice Africa Uganda have nociceptive pain and 24% of both cancer and/or AIDS patients also have neuropathic pain.

An accurate diagnosis of the cause of the pain is therefore essential. Often the patient has several different sources of pain.

The pain may be due to the cancer (e.g. bone metastases, soft- tissue infiltration, nerve compression), treatment-related (e.g. post-operative adhesions), associated problems (e.g. constipation, pressure sores) or unrelated problems (e.g. osteoarthritis).

DIAGNOSIS: THE STEPS TO BE FOLLOWED:

1. DETERMINE THE EXACT SITE AND TYPE OF EACH PAIN by asking the patient to mark the site of the pain on a body chart, taking a history of the pain regarding type of pain, what affects the pain positively or negatively, previous treatments that have helped and then reflecting on the pain in the light of the holistic history and physical examination.

I. Use Body charts: (appendix 1, page 226.)

1. General body chart to indicate site and number of pains. The patient gives this information with the history.

2. Dermatome chart if nerve pain in dermatome distribution (e.g. Herpes Zoster or sciatic type of pain).

3. Indicate on a second body chart, the main physical findings on clinical examination.

II. Take a history of each pain separately:

1. **Character of pain**.

Nociceptive pain may be described as an ache, cramps, like having a baby, throbbing etc.

Neuropathic pain is usually very difficult to describe, especially in societies with many dialects (Africa) where different words may be used to describe the same pain. It is usually described as:

(a) Burning, pricking, paraesthetic or like a feeling of insects biting or crawling

(b) Sharp or shooting.

(c) There may be accompanying sensory changes such as hyperaesthesia, cold and mechanical allodynia – a non painful stimulus being interpreted as painful, (e.g. the examiner's hands being interpreted as very painful in a patient with severe post herpetic neuralgia), and loss of sensation to heat or cold or pain in the affected area.

Remember all of these can occur in the same patient.

2. **Duration of pain.**

3. **Intermittent or steady.**

(a) Usually steady or comes and goes and remains

(b) Usually fleeting but very severe and intermittent indicates convulsive type of neuropathic pain.

4. **Is the pain inside or outside of skin?**

5. **Effect on sleep, mobility and activities of daily living (ADL): gives a clue to severity.**

6. **Types of analgesics tried and effects on the pain.**

If pain was relieved when did it come back? (Possibly when the analgesics were stopped or finished?).

Remember that nerve pain may be partially sensitive to step 1 or 2 of the analgesic ladder. So avoid initial polypharmacy.

7. **Significance or meaning of the pain to the patient e.g. Do they believe the pain is a result of witchcraft/a sign that disease is progressing**

Table 1: The PQRST of Pain Assessment

Meaning		Example
P	Palliative, Provocative	What makes the pain better? What makes the pain worse?
Q	Quality	What are the properties & characteristics of the pain? How would you describe the pain?
R	Radiation	To where does the pain start and then travel?
S	Severity	Rate the pain; on a scale of 0-5, how bad is your pain?
T	Temporal	What are the patterns of the pain? Is it constant, or does it come and go?

Severity:

It is most important to measure the severity of the pain in order to monitor the improvement from analgesics and as an M&E exercise to demonstrate the effects of analgesia on appropriately diagnosed pain.

Measurement tools:

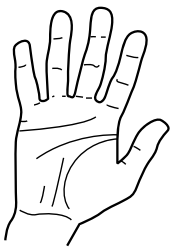
PAIN ASSESSMENT – NUMERICAL RATING SCALE (Visual Analogue Scale) of 0-5.

The Numerical Rating Scale is from 0 to 5

0 being the lowest score = **No Pain**

5 is the highest score = **Worst pain possible**

Different methods of measuring can be used suitable to the cultural context. A full Jerican can indicate the worst pain as 5 and an empty one as no pain. We have found using the five fingers very useful even for children. Others use smiley faces. *(see page 61)*

Use of the five fingers of the hand to grade severity of patient's pain, starting with the little finger upwards:	
	Little finger – Mild Pain, Numerically 1 Up to **Ring** finger – Moderate pain, Numerical score 2 Middle finger – Moderately severe pain, Numerical score 3 Index finger – Severe pain, numerical score 4 Thumb – **Overwhelming pain**; Numerically scores 5 & is maximal

	Pain 1 (*from body chart*) **Score (0-5)**	**Pain 2** (*from body chart*) **Score (0-5)**	**Pain 3** (*from body chart*) **Score (0-5)**	**Pain 4** (*from body chart*) **Score (0-5)**	**Pain 5** (*from body chart*) **Score (0-5)**	**Pain 6** (*from body chart*) **Score (0-5)**	**Pain 7** (*from body chart*) **Score (0-5)**	**Pain 8** (*from body chart*) **Score (0-5)**
Visit 1								
Visit 2								
Visit 3								
Visit 4								
Visit 4								
Visit 5								
Visit 6								
Visit 7								
Visit 8								

IV Diagnose type of each pain as accurately as possible.

Is it nociceptive/normal or neuropathic/nerve pain?

Examples of SOMATIC Pain:

BONE PAIN: Tumour involvement of bone is the most common cause of cancer pain. Any tumor may involve bone; the most common include metastatic cancer of the breast, lung, prostate, and thyroid and multiple myeloma. Common sites of bone metastasis are the vertebral column, skull, humerus, ribs, pelvis, and femur. Bone pain usually present as a dull ache over a large area, and/or a clearly localised area of pain and tenderness over the affected bone. It is described as a constant pain which is usually worse with movement.

VISCERAL PAIN – is usually dull and aching in character and often poorly localized as well as deep-seated. It arises from distension or spasm of a hollow organ such as the discomfort experienced early in intestinal obstruction or cholecystitis.

HEADACHE OF CEREBRAL METASTASES OR CRYPTOCCOCAL MENINGITIS – described as "dull", "oppressive", "vice-like" and characteristically worse on wakening or in the late evening. Is there raised intracranial pressure? Photophobia or projectile vomiting with or without nausea? Meningeal irritation with neck stiffness?

MUSCULAR PAIN OR SPASM – often associated with underlying bone metastases.

1.5 NEUROPATHIC Pain:

Examples of NEUROPATHIC Pain:

NERVE COMPRESSION PAIN DUE TO AN ADJACENT TUMOUR localised to one or two dermatomes, often described as an "aching" or "stabbing" pain.

DYSAESTHETIC PAIN DUE TO NERVE OR NERVE ROOT INFILTRATION BY CANCER, HIV OR HERPES ZOSTER – described as "discomfort", "burning", "numbness", also localised to one or two adjacent dermatomes.

HYPERAESTHESIA OF THE SKIN

A generalized increased sensitivity in the skin felt on light touch, relieved by firm pressure and found in patients with malignant melanoma, small cell carcinoma of the lung and advanced Hodgkin's Disease and AIDS.

Consider the cause of each pain and if possible, treat underlying cause e.g.

Peripheral neuropathy due to ARVs (pain onset after time of commencing ARVS)- Refer to their ARV centre for opinion re changing ARV regimen.

Peripheral neuropathy due to damage to nerves by HIV- If patient not on ARVs, consider referral for ARVs (but describe their pain, so appropriate ARVs can be chosen).

Infections e.g. chest infection causing pain – use antibiotics

Oral pain due to candidiasis – use fluconazole

Tumour pressing on a nerve or malignant bone pain – consider short-term dexamethasone and radiotherapy

Herpes zoster – if available and affordable consider acyclovir.

> Tip: Consider sap from Frangipani tree for zoster pain (see p 61)

Symptomatic treatment of the pain can go hand in hand with treatment of the cause.

Only when the sources of the pain have been defined, can the appropriate management of that pain be considered. However pain cannot always be accurately diagnosed. In such cases it is usually possible to define as somatic or neuropathic and appropriate treatment commenced.

The management will include:

1. A clear explanation of the problem to the patient.

2. The use of appropriate analgesics.

3. The use of specific treatment modalities when available and affordable. These include the following:

a) In cancer: surgery, radiotherapy, hormones, cytotoxic drugs only in the light

of the patient's general condition and likely prognosis.

b) In AIDS concurrent use of antibiotics, antifungals and anti retroviral therapy maybe appropriate if affordable and available. (See section III)

IV. Choose an analgesic regime appropriate to each type of pain.

SELECT DRUGS with minimal side effects and compatible with others used.

CHECK and re-check regularly, whether adjuvant drugs are appropriate for new problems developing.

TAKE TIME TO EXPLAIN every detail to the patient and relatives involved in care and all associated colleagues, medical and nursing. REVIEW the regimen regularly.

Gives some idea of the complexity of treatments available in resource rich countries. However medical management is often the only available treatment in many of the poorer African countries. Because of late presentation of cancer patients, using surgical techniques to alleviate neuropathic pain leaves the patient with the same requirements of medical treatment and surgical intervention may be expensive and lead to poorer quality of life.

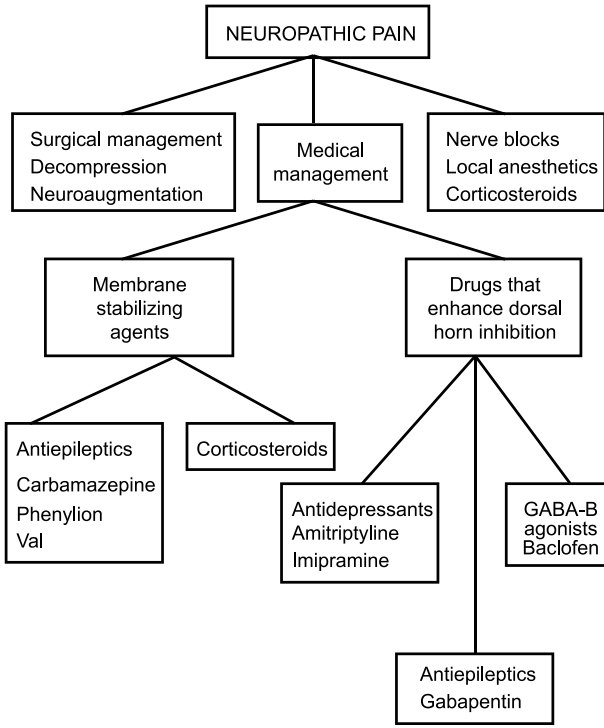


Figure 5 : Algorithm for treatment of neuropathic pain[6]:

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6 M. Sam Chong, and Zahid H. Bajwa, *Journal of Pain and Symptom Management.*` Vol. 25 No. 5S May 2003

1.6 MANAGEMENT OF NEUROPATHIC PAIN:

Remember that neuropathic pain is only partially responsive to the drugs of the analgesic ladder. However if commencing with the analgesic ladder then should wait to see if there is any response before commencing the adjuvants described below. Spontaneous pain (burning, aching) usually as a result of sensitized nociceptors, may respond well to opioids.

Based on the neuronal mechanisms involved in neuropathic pain, any treatment that can reduce hyper excitability is likely to be of value.

TRICYCLIC ANTIDEPRESSANTS have been used to manage neuropathic pain for over 30 years. Action is through enhancement of dorsal horn inhibition. They are of benefit in controlling dysaesthesia caused by nerve and nerve root infiltration by tumour or HIV. e.g. Amitriptyline commencing with a dose of 10-12.5mgs nocte. In our experience the relief is dose specific, and gradual increase of dose is indicated if pain is not improved in 3 days. Large doses may not help the pain so gradual increase is essential together with daily assessment. Side effects are minimal in our experience, when dose is titrated starting with a very small dose of 12.5mg o.d – bid. An effective dose is usually under 25mgs once daily

ANTICONVULSANTS:

`Anticonvulsant' is a term used for a series of compounds originally introduced for the treatment of epileptic seizures, but with a variety of other mechanisms of action. In addition to their antiepileptic properties, anticonvulsants have also been used to treat various chronic pain conditions, in particular neuropathic pain.

Carbamazapine and phenytoin were the first to be used in the treatment of trigeminal neuralgia based on the idea that the temporal profile and abrupt nature of the painful attacks were similar to those seen in seizures.

Phenytoin, carbamazepine, among others, have been shown to reduce ectopic discharges from injured nerve endings and dorsal root ganglion neurons by a sodium channel-blocking action.

Phenytoin:

Phenytoin exerts its membrane-stabilizing effect by blocking sodium channels, a mechanism by which it reduces neuronal excitability of pain fibres, thus helping in controlling stabbing, dysaesthesia (abnormal sensation) pain.

Phenytoin is readily available and affordable in most developing countries and it works!

Initial dose is 100mgs bd, increasing slowly to 400mgs if not relieved.

Toxicity has not yet been seen in these doses used in Uganda. However with the advent of ARVs there is need for care.

It has significant drug interactions with particular ARVS e.g. nevirapine (Though appears to be more of a risk of phenytoin effectiveness being reduced by ARVs rather than vice versa). It should either be avoided in patients on ARVs, or one should check whether there is a specific interaction between phenytoin and the specific ARVS a person is taking.

Carbamazepine:

Carbamazepine has been used since 1960s for trigeminal neuralgia and has been shown to be effective in some other neuropathic pain syndromes e.g. diabetic neuropathy. It is more expensive than phenytoin and requires laboratory white cell monitoring which many patients cannot have access. It also has more side effects such as nausea and has more drug interactions because of liver enzyme induction. Because of the monitoring required and side effects we do not recommend it for routine use in our situation. It also has interaction with ARVs.

Starting dose: 100mg BD gradually titrating over weeks to a usual maintenance of 400-1000mg/day

(efficacy has been seen in variety of trials with dose range 300 - 2400mg/day)

(One source of such information is ATIC -

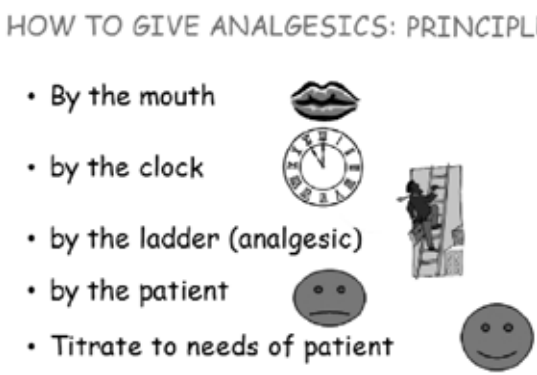
AIDS treatment information centre based in IDI, Kampala). Health workers in Uganda and other countries can email at *queries@atic.idi.co.ug* to send in queries from Uganda or other African countries).

Medical management is often the only available treatment in many of the poorer African countries. Because of late presentation of cancer patients, using surgical techniques to alleviate neuropathic pain leaves the patient with the same requirements of medical treatment and surgical intervention may be expensive and lead to poorer quality of life.

1.7 PRINCIPLES OF PAIN CONTROL:

How to take analgesics with constant and increasing pain:

The Analgesic Ladder Approach includes the following advice:



Medications must be given:

By the ladder

By the mouth (so possible for analgesia at home)

By the patient

By the clock (or by the sun if they do not have a clock).

THE ANALGESIC LADDER USED FOR SOMATIC TYPE PAIN:

THE ANALGESIC LADDER:

Analgesics available in Uganda used in cancer and/or AIDS pain

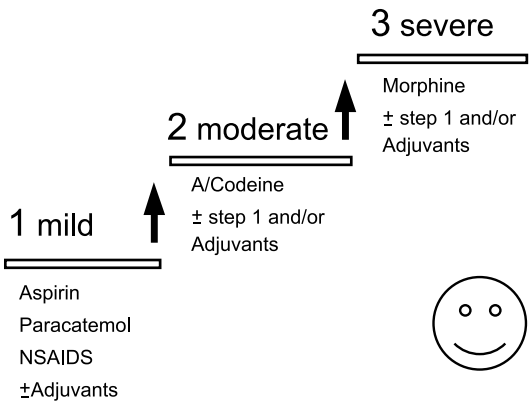


Fig 6: WHO 3-step Ladder

Adapted with permission from EPEC, North Western University, Chicago, US

Table 2: The half life of a single dose of some

commonly used oral analgesics in the pain of advanced cancer and/or AIDS.

Note: after about five half-lives at the same dose and frequency a medication reaches "steady state" in the body; Implication eg: 5 half lives on a constant dose of oral morphine (20hours) means at the end of one day (24hrs) that is maximal analgesia possible at that dose& if patient is still in patient the next day the dose needs to be titrated upwards

DRUG DURATION
aspirin 4-6 hours+
paracetemol 4-6 hours
ibuprofen 6-8 hours
diclofenac 8 hours
codeine 4-6 hours
** Morphine solution 4 hours
** MST 12 hours
Available in Uganda 2012
in the elderly or those with reduced renal function morphine and codeine may last longer

* Available from JMS 2012

** Available in JMS and on Essential Drug List in Uganda 2012

Aspirin not recommended for prolonged use

in terminal cancer because of side effects

Codeine and step 1 analgesics have ceiling effect above which increasing the dose does not provide more analgesia.

As the patient's pain becomes more severe, he or she will need a stronger analgesic. Should step 1 be inadequate then step 2 can be added. In turn when a step 2 is no longer of benefit then a step 3 should be substituted for step 2 while maintaining step one.

However in cancer patients with progressive pain, it is reasonable to leave out step 2 and go directly to morphine in step 3. This is because of the expense of codeine, and also the patient has to go through more pain during the change over from step 2 to 3.

An analgesic should be prescribed according to its known duration of effectiveness (See TABLE 2), ensuring that the pain is constantly controlled and never allowed to re-emerge. There is no place for prescribing analgesics on an "as required" or "prn" basis.

Note: [Analgesics not available presently in Uganda not included]

NSAIDS

These are the most common medications used in palliative care. Thus the cost is critical to the budget of the service. The cost should be worked out for a week's course. For example in Uganda, on going to press, ibuprofen is the cheapest per tablet but Diclofenac sodium

is the cheapest for a course because of the longer half-life. It is important to watch the prices in an ongoing service. The choice of which of the NSAIDS to prescribe will depend on the availability and tolerability.

SIMPLIFIED THERAPEUTICS OF MORPHINE:

Morphine, is absorbed from the ileum when taken by mouth and the majority then passes through the liver. Buccal absorption follows a similar path.

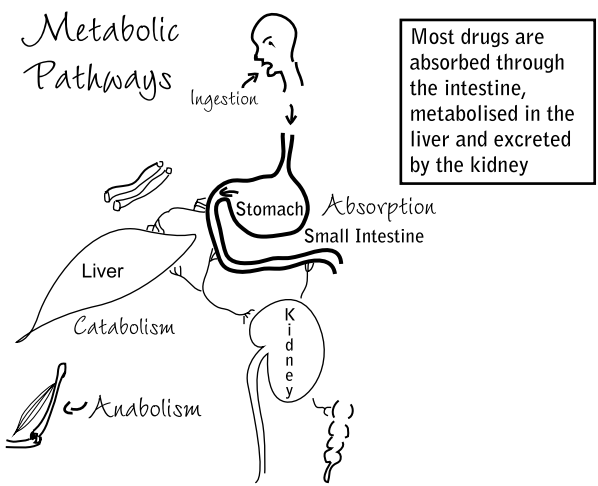


Figure 7: Metabolism of drugs e.g Morphine

The liver metabolises morphine into a very potent metabolite for pain control, M6G. This is more potent than morphine itself. When

taken orally on a regular basis, a level of M6G is reached in the body allowing freedom from pain. The liver needs to have at least 90% damage before it is unable to metabolise morphine.

Morphine is excreted through the kidney. Care must therefore be taken in renal failure, old age and the last days before death. In such cases morphine interval may need to be longer or the dose reduced. If there is no urine output, then morphine may need to be stopped altogether and given prn. This is the only time when prn is allowed!!

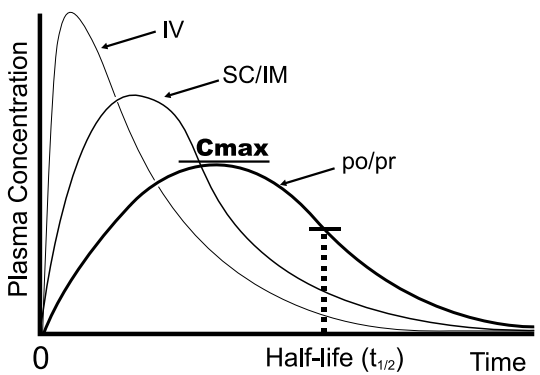


Figure 8:

It can be seen from the figure 8 (courtesy of EPEC, US) that because of the shorter time to reach CMax, lower level at ½ life, and because a smaller proportion is metabolised in the liver, these routes are not as effective in building up M6G and maintaining a level.

It is essential that pain is not allowed to

return as much as possible for our patient. Oral morphine is given 4 hourly and figure 5 illustrates how this is achieved with regular doses keeping pain control without side effects.

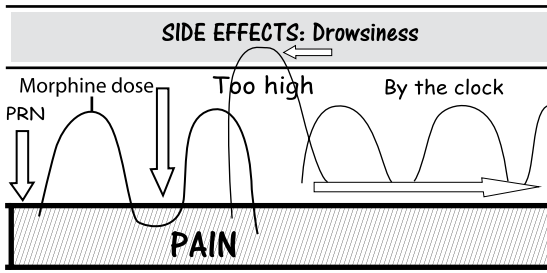


Figure 9: Illustrates how the side effect of drowsiness alerts us when the dose is now too high.

1.8 THE USE OF OPIOIDS

The second step analgesic usually available in Uganda is the mild opioid, codeine. This has increased in price very much and so is usually unaffordable. So we are presently prescribing low dose morphine in patients with pain, foregoing the second step of the ladder. A weak opioid – codeine, is as effective as a small dose of morphine because codeine is a pro-drug of morphine. Thus, step 2 analgesics are pharmacologically "not necessary". Each country needs to assess the prices for affordable pain control.

Morphine is dispensed as a liquid made up with a preservative (bronopol) to a concentration which must be specified by

the prescriber - e.g. usually 5mg/5ml and 50mg/5ml etc. (Prescription: see appendix 2, formula: Appendix 3a).

This has a shelf life of 6 months[7] and is sufficient for those using it on a daily basis.

STRENGTH	COLOUR
5MGS/5 ML	GREEN
50MGS/5 ML	PINK/RED
100MGS/5 ML	BLUE

Fig6: Strengths and Colour codes recommended for Africa

For safety sake we are trying to standardise the strengths and colour codes in Africa as shown in figure 6. This is because increasingly, patients are crossing borders seeking speicalised treatments.

Usual strength dispensed is 5mgs per 5ml (green), but in the few patients requiring larger doses, the 50mgs per 5ml (red) may be more convenient. A 100mg per 5ml (blue) strength of oral morphine is currently available in Uganda, made up on special request. Other countries with a dedicated pharmacist can make up similar strengths.

7 HAU is in process of formally extending shelf life to 12 months following tests on the product made up using the formula we have& in the tropical Ugandan conditions.

The usual starting dose is 2.5-5mg 4-hourly and a double dose at bed time. The lower dose of 2.5mg 4-hourly may be considered in the frail and/or elderly patient.

For the patient who has been taking an alternative strong opioid, the equivalent dose of morphine should be used. However, there are presently no such alternatives in Uganda (2011) apart from pethidine which is unsuitable.

MST is available at Hospice Africa Uganda as 10mg, and 30mg tablets, (courtesy of NAPP, UK). These are slow release morphine tablets and the total daily dose is the same as the total amount of solution used in 24 hours. e.g. 10mgs 4 hourly, is equivalent to 60mgs per day, i.e. 30mgs MST bid. (see below).

Although liquid morphine must be prescribed 4-hourly, most patients do not require a dose in the middle of the night. The patient takes a double dose at bedtime before settling and this ensures an undisturbed night and prevents having to wake for a 4 hrly dose. If taking more than 60mg of morphine 4- hourly, some patients find one-and-a-half times the usual dose before settling is sufficient. However in our experience in Uganda, most patients are taking less than 60 mgs per day with complete pain relief. However it must be stressed that every patient and every pain is different and *opioids should not be withheld because their suitable dose is too high.*

The dose should be titrated against the patient's

pain and regular review is important. Starting dose depends on the age and condition of the patient. The aim is for the patient to be free from pain but able to think and perform normally. A typical 4 hourly incremental scale is: 5,10,15,20,30,50 until pain is completely controlled without drowsiness, which is the goal for all patients on morphine.

1.9 SIDE EFFECTS OF OPIOIDS:

1. NAUSEA AND VOMITING - It is reported in the literature that a third of patients when taking morphine will suffer nausea and vomiting initially, which is self limiting to about 5 days. This problem is rarely seen in African patients in our own study and observations. This may be due to the low doses we commence with or due to a different metabolism of the drug in Africans. This is an important area requiring research. If it occurs, nausea can be controlled by anti-emetics such as metoclopramide 10mg 8-hourly, haloperidol 0.5mg 12 hourly no longer than 5 days.

2. SEDATION may occur but only in the first few days. This may be due to overdosing with morphine, but more often is due to lack of sleep for months due to uncontrolled pain! If it persists more than 2 days, the dose should be titrated back until patient is alert and pain controlled.

3. CONSTIPATION - inevitably codeine and morphine cause constipation and a laxative should ALWAYS be prescribed as a

prophylactic (Care in AIDS patients who are susceptible to diarrhoea). This should be a combined pusher and softener. However laxatives are quite expensive and sennokot, which is cheap in the West, is expensive here. It is from the senna coffee tree, which could be grown and distilled for use (research needed). The cheapest laxative available is bisacodyl 10 mgs (2-5 at night) but it can cause cramps in the constipated and frail patients. Then start with 1 tab bd and slowly increase, titrating against results. Many patients have a favourite herbal medication, which has worked for them for years. This can be used if it is harmless and not too severe. Crushed paw-paw seeds also have a laxative action. They are bitter to chew but they are acceptable to many, and cheap and available. It is important not to swallow the seeds whole as the ingredient is inside and the seeds can pass through without the effective ingredient becoming available. Crushed dried seeds can be taken in yogurt or porridge. 1 teaspoon of crushed seeds can be used initially and increased up to five fold at night. Other methods if available are e.g., Sennokot 2 - 5 at night may be followed by bisacodyl suppository after breakfast following morning if no urge to pass stool.

Ask the patient if he/she has ever taken a herbal laxative in the past and if it was useful, and had no harmful side effects, encourage to use.

4. MYOCLONIC JERKS, HALLUCINATIONS AND NIGHTMARES – rare in Uganda.

Usually indicate opioid toxicity and are often improved by hydration, and dose reduction. If not responding, in countries where available, switch to an alternative strong opioid.

5. RESPIRATORY DEPRESSION is not a problem provided the patient is commenced on a small dose initially 2.5 - 10mg) and the dose then titrated, according to the pain (see above).

6. ADDICTION and TOLERANCE are not problems of any practical importance, in the use of oral morphine for the pain of advanced cancer. Physical dependence can develop when used for prolonged periods, and morphine should be discontinued carefully, if additional forms of treatment such as radiotherapy or a nerve block relieve the pain (see below).

In AIDS temporary severe pain eg. Cryptococcal meningitis, strong opioids have been withdrawn without any problem after treatment of the infection. The patient becomes drowsy as the pain becomes less, an indication that the morphine can be reduced or discontinued.

1.10 SOME MYTHS ABOUT MORPHINE THAT MAY PREVENT ITS USE:

RESPIRATORY DEPRESSION: this is unknown in our experience when using small doses of oral morphine titrated against pain. However it has been reported in Uganda

when a health professional, inexperienced in palliative medicine advances and the use of oral analgesics, prescribed morphine 10mgs parentally 4 hourly in a morphine naïve patient. *It is very important that even doctors, undergo training in the use of oral morphine before prescribing it.*

Respiratory depression has been reported in a case in UK, when pain was completely removed by a nerve block, even when morphine was decreased slowly (Twycross, 1988). This also proved that pain is a physiological antagonist to respiratory depression.

Also, sedation occurs before respiratory depression. As morphine is mostly given orally respiratory depression is rare as a somnolent patient swallows less. Because of the comparatively short half life of morphine stopping further opioid administration, ensuring hydration for renal elimination, and supportive patient management (rather than naloxone) will often be adequate interventions needed to prevent toxicity.

TOLERANCE: Increasing dosage of morphine is the accepted method of titrating morphine against the pain until the pain is controlled. The only upper limit is the dose that controls the pain while the patient is still alert.

ADDICTION: Addicts are looking for a high, which cannot be obtained when morphine is taken by mouth. This is only obtained with IV administration. Pain is now known to be a physiological antagonist to addiction. In a

study in US in 1989 of 11,882 patients on therapeutic morphine for pain, only four were found to be addicts[8].

COGNITIVE IMPAIRMENT: There maybe some sedation when morphine is first commenced, but this is temporary, lasting 2-3 days at the most. The patient on morphine should be alert and feel normal, able to eat sleep and attend to normal affairs without impairment.

LETHALITY: morphine does not kill when properly prescribed and gradually increased according to need. Patients have been shown to live longer because they eat, sleep and live normal lives. Morphine can kill if given in large doses especially with parenteral administration, in a naïve patient to morphine[910].

OTHER ORAL ALTERNATIVES TO STRONG OPIOIDS

Other step 3 analgesics are available in richer countries and from time to time are available in limited amounts and at expensive prices in Uganda. Many physicians try to use these in their efforts to avoid morphine due to erroneous beliefs regarding addiction (see

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8 Porter J, Hick H: Study of addiction in patients treated with narcotics, New England Journal of medicine, 1989, 302:123

9 Farley J. The Comfort Zone: Effective Pain Management, 1998.

10 *N Engl J Med 2010;363:733-42.*

above). Sadly some drug firms capitalize on this. We hope that the explanations given above will assist health workers to work with affordable products.

One such drug on the market recently in Uganda is Tramadol hydrochoride. This is marketed for moderate to severe pain (step 2) but has a ceiling and many side effects, which must be monitored (see BNF). It is not recommended for long-term use. Dose should not exceed 400mgs per day and is usually 50 mgs 4-6hrly.

ANALGESIC	Potency Ratio	Duration Hrs
Codeine/ dihydrocodeine	1/10	3-5
Tramadol	1/5	5-6
Tramadol im	1/10	4-5

Others occasionally required can be researched e.g Hydromorphone. Fentanyl. Methadone, bupenorphine)

For further information on other step 3 analgesics, readers are referred to the Formulary for Palliative care[11] and British National Formulary.

1.11 INCIDENT PAIN and BREAKTHROUGH PAIN:

MANAGEMENT

Incident pain (severe pain precipitated by a particular procedure, changing a dressing, catheterisation, disimpaction, etc.) requires prompt treatment. The regular analgesic

11 Twycross R, Wilcock A., PCF4 Palliative Care Formulary fourth edition: Strong opioids, page 345

regime can be supplemented by:

An additional oral dose of morphine one hour before a procedure or a subcutaneous dose (1/3 of oral dose), given 30 minutes before the procedure if a heath worker is available e.g. in a health centre.

A regular additional dose of oral morphine (same dose) should always be prescribed for *breakthrough* pain with instructions left clearly with patient and relatives, to give as soon as pain is detected and not to wait for it to become severe, when it can be more difficult to control. At following visit the number of breakthrough doses is noted and new increased regular doses calculated to include the total needs in 24 hours and dividng by 6 to give the 4 hourly dose with a double dose at night.

STRONG OPIOIDS: ALTERNATIVE ROUTES OF ADMINISTRATION:

Oral to parenteral ratio for morphine is 3:1.

NOTE *the exceedingly small doses of morphine used to control pain.*

WARNING: always check the oral dose and divide by 3 before giving the equivalent therapeutic dose parenterally.

Ideally the oral route should be used whenever possible. However, if the patient is vomiting or unable to swallow due to the obstructing effects of a tumour in the mouth, pharynx,

oesophagus or stomach, strong morphine can be dripped in the correct dose, into the mouth and absorbed by the buccal mucosa. Very occasionally an alternative route is needed.

SUB-LINGUAL or BUCCAL ROUTE

Morphine solution, like any medication soluble in water, is absorbed from the buccal mucosa and can be given in the moribund or vomiting patient by the family. Because absorption is variable, a larger dose may be required in different individuals. This can be specially made up as blue morphine to allow the same dose in a smaller volume. It can also be used in obstruction in concentrated form, and held in the mouth. Rectal long acting tablets may give smoother control if they are available (see below).

RECTAL ROUTE

MORPHINE suppositories - like morphine solution - must be prescribed 4-hourly. Because *most patients object to 4 hourly rectal administration we use* MST tablets given 12 hourly by rectal route.

INJECTIONS

When a patient is unable to swallow, we are able to keep them comfortable using either buccal morphine dripped into the mouth or by suppositories.

Morphine by injection, in the home, is not practical and we have found in Uganda that

the morphine pumps are scary to the patients and they do not manage them well. We have not used them now for 16 years and kept our patients comfortable in the home by other means.

MORPHINE, may be given subcutaneously 3 to 4 hourly (there is no need to give the injection intra-muscularly). Injection volumes need only be very small, and the smaller the injection, the less painful. It is available commercially in Uganda as 10 & 15mg/ml.

This is used rarely, if buccal drip not possible, when the patient is unable to take oral drugs because of:

nausea and vomiting

intestinal obstruction due to malignancy

dysphagia

diminishing conscious level.

In addition, morphine by injection can be given to control severe and overwhelming pain and breakthrough pain associated with painful procedures. However oral morphine has proven equally effective when it is used for children with burns, given 30-60 mins before changing dressings.

It must be remembered that intravenous morphine has a short half life because of the rapid by pass of the liver. and results in less effective pain control and escalating doses. (see fig 4)

SUBCUTANEOUS CONTINUOUS INFUSION OF MORPHINE:

Very occasionally this may assist when a patient unable to swallow is going home to the village with a short life expectancy. A syringe containing morphine can be strapped to the arm with an sc needle, butterfly or Teflon IV catheter inserted. The family is shown how to inject a small amount every 4 hours. Most patients unable to swallow can be assisted with buccal or rectal administration.

Our experience in Uganda over 18 years has shown that we can keep the patient comfortable even when unable le to swallow, using buccal (best) or rectal morphine. Rectal slow release morphine 12 hourly is most acceptable and carer can be shown how to insert.

Those interested in subcutaneous continuous infusion pumps are referred to appendix 4.

1.12 ADJUVANT DRUGS (CO-ANALGESIC)

Various drugs can help complement the analgesic ladder when used in control of pain in advanced cancer. Which adjuvant drugs should be used depends on the precise cause of the pain.

Step 1: (analgesics not adjuvants). These NON-STEROIDAL ANTI-INFLAMMATORY DRUGS are often of benefit in the control of pain due to bone metastases. Pain due to stretch of a membrane (periosteum, peritoneum, pleura,

pericardium) or skin, inflammation and soft tissue infiltration are due to the release of prostaglandins at the nociceptors (see page 13). Thus step 1 analgesics are also known as anti prostaglandins, except paracetemol.

Although there are many drugs in this particular group it is best to become familiar with a small number. As patients vary in their response to NSAIDS, it is good to change to another if the response is reduced. If pain is not relieved after trying two or three, then consider it not sensitive to NSAIDS and revisit diagnosis.

STEROIDS can also assist with the above pains as well as helping in the control of pain caused by nerve and nerve root compression by tumour (by reducing the inflammation around tumour) and the headache caused by raised intracranial pressure. Dexamethasone, as it is so much more potent (by a factor 7) than prednisolone, is the steroid of choice. The dose varies with the condition being treated (see under AIDS pain).

To avoid any long term side effects the dose should be reduced gradually over the following 2 - 3 weeks. Should it prove to be of no benefit then the drug should be discontinued.

MUSCLE RELAXANTS can help when the pain is due to muscle spasm, often associated with underlying bone metastases or paraplegia. Try lorazapam 1-2mgs, diazepam 5- 20mg nocte initially, then move to baclofen

5–20mgs tds. Muscle spasms are difficult to control, particularly in paraplegia and require the holistic approach and counselling.

Acute cramps in muscles can be very painful and can be controlled in some by quinine tabs 300mgs daily for 3 days then commence again if they return.

ANTIBIOTICS will help pain caused by opportunistic infections, abscesses etc.

TOPICAL ANTIBIOTICS: These are generally not very useful and can cause sensitivity. However the pain and smell caused by an ulcerated malignant tumour (anaerobic bacteria in dead tissue) is alleviated by topical metronidazole. Metronidazole tablets are crushed and sprinkled on the wound. It does not respond to oral metronidazole because there is no blood supply to dead tissue.

1.13 OTHER MODALITIES OF TREATMENT

PALLIATIVE RADIOTHERAPY

Palliative radiotherapy (if available) plays an important part in the control of pain due to tumours. Single dose treatment for pain in bone metastases is as good as fractionated doses. Most respond within a few weeks. The discomfort and risk of bringing the patients to the radiotherapy department along bumpy roads in Africa have to be weighed against the benefits. Extension of a tumour into bladder or bowel is a relative contraindication for radiotherapy because of the danger of

fistula formation. It can be very effective in reducing soft tissue ulceration and bleeding.

EMERGENCY RADIOTHERAPY

Pain with symptoms indicating imminent cord compression is an indication for emergency radiotherapy i.e. within 24 hrs if possible or as soon as possible The rationale is to try to save the person's ability to walk and to be continent. If left untreated it will result in paralysis and loss of sphincter control. High dose dexamethasone (16-24 mgs) should be given at time of diagnosis of likely cord compression and continued throughout radiotherapy, tapering gradually afterwards.

Similarly for acute superior vena cava obstruction (SVCO), high dose dexamethasone should be given immediately. If available, radiotherapy may help if not responding to dexamethasone.

HORMONE THERAPY

For patients with hormone responsive tumour (breast and prostatic cancer in particular) hormonal manipulation has an important contribution to make in the control of pain. The commonest treatments used at present are: stilboestrol 1-5mgs for prostatic cancer or tamoxifen 10-20 mgs daily for breast cancer. Both are outside the budget for 90% of our patients.

Surgical castration is more affordable and slows progress in some patients with rapidly advancing prostatic carcinoma. However

it is often refused because of the sexual implications and possible feminisation attached.

CYTOTOXIC CHEMOTHERAPY

By reducing tumour bulk cytotoxic drugs can help in the control of pain.

SURGERY AND ORTHOPAEDIC PROCEDURES

Amputation of a tumour bearing limb or organ may be possible and relieve pain. However phantom limb pain is fairly common post amputation and should be treated as for neuropathic pain (see above). Surgery also includes toilet mastectomy for pain and ulceration.

Prophylactic internal fixation of a weight-bearing bone (when a pathological fracture through a large metastasis is likely) can help in controlling the pain due to the metastasis.

The value of operative procedures must be weighed against the condition of the patient. Surgery is contraindicated in stage 4 AIDS because of delayed healing and breakdown of wounds.

NERVE BLOCKS:

These are not possible in most African countries as yet. However as most of our patients do not have access to chemotherapy or radiotherapy, they present with multiple pains, all of which need to be diagnosed and

treated. Isolated or resistant nerve pain is rare.

1.14 PAIN IN AIDS:

COMMONEST AIDS PAINS AND THEIR MANAGEMENT AT HOSPICE UGANDA:

Wherever possible alongside pain management give relevant antibiotics or anti fungals.

1. CRYPTOCOCCAL MENINGITITIS:

Raised intra-cranial pressure Headache: normal intra-cranial pressure

Raised intracranial pressure

Use analgesic ladder.

Unlike ICP due to brain tumours, the headache associated with ICP due to cryptoccal meningitis does not respond well to dexamethasone and there is one study which showed poorer outcome in those patients receiving steroids. It is best to treat with regular analgesia e.g. morphine, while simultaneously treating the infection. (In hospitalized patients lumbar punctures are helpful in reducing pressure).

Normal intracranial pressure

Treat with analgesic ladder.

2. MUSCULO SKELETAL PAIN:

Treat with analgesic ladder. Usually responds to STEP 1 or STEP 1+ STEP 2/3. The severe

pain of multiple pyomyositis requires analgesia along with incision, drainage and antibiotics.

3. NEUROPATHIC PAIN: see also pages 22-27

It is essential to diagnose correctly as chronic types of Neuropathic pain are not usually fully responsive to the analgesic ladder.

There are two clinical categories of neuropathic pain here detected as

(a) Dysaesthesia, paraesthesia, burning or pins and needles

(b) Severe sharp or shooting pain with relatively no pain in between.

Analgesic treatment is based on accurate diagnosis.

TREAT THE PAIN:

If patient is commencing on morphine for another pain, wait a few days and reassess nerve pain as it may be somewhat relieved.

(a) Paraesthesia or abnormal sensation: treat with amitryptiline starting with 12.5 mgs bid or 25mgs at night. *There is a window effect in some patients so larger doses may not effect the pain. We rarely need more than 25mgs per day in Uganda.*

Pain should be relieved in 1-5 days.

(b) If sharp or shooting in character

commence anticonvulsant phenytoin 100mgs bid to 200mgs tds, but be aware of potential drug interactions- see section….Again start with the lesser dose. Pain should be relieved within 24 hours: if no, or poor response, try amitryptiline.

TREAT THE CAUSE:

AIDS infections: treat infection

If swelling around a tumour, treat with a steroid, e.g. dexamethasone (decreases inflammation and reduces size in confined space).

Dexamethasone can also reduce inflammation in nerves.

Use in conjunction with antifungal treatment because of immuno-suppression in terminal disease.

TREAT HOLISTICALLY:

As in all pain, neuropathic pain is worsened by other factors. These include social, spiritual, psychological and cultural aspects. These must be addressed, especially if pain is not improving. Quality time with the patient, by a dedicated health professional is very valuable.

Tip for Acute Herpes Zoster:

Liquid from frangipani tree when applied to the vesicles causes paralysis of the sensory nerve endings for up to 8 hours. Break off a small branch and collect the white fluid into a clean jar. Paint this onto the area. Fluid lasts 24 hours. Apply 8 hourly. Although initially painful on open vesicles, it also controls pain at this stage.

4. OESOPHAGEAL ULCERATION:

Cause not usually identified but always has an element of candidiasis.

Many patients are extremely emaciated because of failure to eat for several weeks. Treatment of symptoms can be life saving!

1. Reduce inflammation by giving steroids. E.g. Dexamethasone 16mgs i.v initially. By the second day the patient can usually swallow. Then give orally so that the dexamethasone can actually touch off the ulceration and remove the inflammation. Reduce by 2 mgs daily.

2. Always give antifungals along with steroids. If resistant to usual antifungals, use clotrimazole pessaries (for both sexes) 500mgs to be *sucked* daily for 5 days (call them lozenges or patient may be put off!!). This usually works and prevents multiplication of the fungus during therapy.

3. Use analgesic ladder if pain is very severe initially but it will reduce after the first day of steroids.

5. MOUTH/VULVAL ULCERATION:

This is very painful and usually due to the herpes simplex virus.

MANAGEMENT:

1. A solution containing: 5mls of nystatin (500,000 units), 2 tablets crushed of metronidazole (400 mgs) and 1 capsule of acyclovir, can be painted to the ulcers twice daily. Pain is usually relieved by the second day and healing follows. This is often affordable. (see page 97 for formula)

2. Acyclovir can reduce the healing time if available and affordable. Oral and topical preparations are available. Apply to the ulcer.

3. If none of the above available then crush a tablet of prednisolone and apply the powder to the affected part to relieve the pain.

4. Gentle mouthwash or douches using a simple antiseptic like 0.05% chlorhexidene can aid oral hygiene.

6. SKIN RASHES in HIV :

Due to opportunistic multi infection of the skin.

Early in the HIV trajectory and itchy: Use 1% hydrocortisone crème as it can change the early immune response.

Later: Rinse total skin in 0.05-0.5%

chlorhexidene twice a day after bathing.

7. OTHER:

Diagnose the pain as accurately as possible and treat as somatic or neuropathic pain as for cancer.

1.15 PAIN IN CHILDREN[12]

Common barriers to effective pain control in children include:

In Africa, crying in children often does not give cause for alarm.

- The mistaken belief that children do not perceive pain in the same way as adults. Nerves transmit pain signals in neonates as young as 24- to 26-weeks gestation.
- Younger children may be unable to report pain. Assessment needs to include observation and carer report.
- Lack of awareness of role of simple non-drug therapies.
- Lack of awareness of impact of emotional/social spiritual concerns on a child's pain experience.
- Lack of knowledge among medical staff about pain relief in children. Misconceptions about the safety of opioids and exaggerated fears of drug addiction.

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12 Adapted by Dr. Nicky Bailhache from WHO, Cancer Pain Relief in Children, Geneva:WHO, 1998

- Children are **not** more easily addicted to opioids

- Failure to reassess regularly.

Pain can have devastating effects, both physically and psychologically, on children with cancer (and AIDS) as well as other disorders such as sickle cell, acute emergencies such as burns etc. Health professionals and parents need to realise the trauma associated with certain kinds of administration of treatments and avoid such routes, e.g. injections. At all times the psychological stage of development of the child must be taken into account.

Honest explanations of management and answering the child's' questions, in a way appropriate to their age and understanding, is a vital part of managing pain and therapy.

Figure 10: FACES pain scale for children

Smiley "faces" scale has been widely used for children aged >4 years

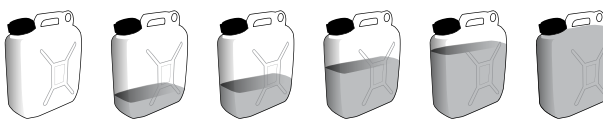
It is simple & quick to use.

Young children tend to use extremes of the scale.

- Some children confuse it with

happiness- they need to understand that the unhappy faces represent increasing pain. Initially they may need an explanation each time it is used, but after a few times they usually understand straightaway and enjoy using it.

- Most preferred scale for 3- 18 years
- African children who are not looking at picture books may fail to recognise faces because unable to see 3D.
- Alternately, use pictures of Jerry cans from empty (0) full can be used with full being the worst pain and graduating the filling 1-5.



0	1	2	3	4	5
No pain	Mild pain	More pain	Moderate pain	Severe pain	Over-whelming pain

WHO ANALGESIC LADDER FOR CHILDREN

Step 1: Non-opioid +/-adjuvant e.g. paracetemol 10-15 mg/kg every 4-6 hours, or ibuprofen 5-10 mg/kg every 6-8 hours

Step 2: Mild opioid +/-adjuvant, +/- Step1**.** e.g. starting dose: codeine 0.5-1 mg/kg every 3-4 hours (best left out in cancer)

Step 3: Strong opioid +/-adjuvant, +/-

Step1**.** e.g. starting dose: morphine 0.15-0.3mg/kg every 4 hours.

Titrate against pain and side effects as for adults. (*in infants less than 6 months the pharmacokinetics of opioids are different and the dose should be reduced by 1/3 to1/4)*

Flow Chart for relieving Pain in Childhood

Assess the child

Conduct physical examination Determine primary cause(s) of pain

Evaluate secondary causes (environmental and internal)

Develop treatment plan

Management of opportunistic infections (with anti-cancer therapy, if available)

Analgesic drugs and other therapy:

By the Ladder Supportive

By the Clock Behavioural

By the appropriate route Physical

By the Child Cognitive

Implement plan

Assess child regularly and revise plan as necessary.

Children do not volunteer to report side effects and should be asked about specific common problems such as constipation, pruritis etc.

Non drug modalities such as distraction, attention, imagery, relaxation and

behavioural management can enable children to understand what is happening and to lessen anxiety.

"Most children throughout the world should receive pain relief and palliative care." Kathy Foley, MD, Chair, WHO Expert Committee on the Comprehensive Management of Cancer Pain in Children.

No one should have to witness and remember that the child's final days were filled with physical pain.

Adjuvant drugs for children

MEDICATION	INDICATION	DOSAGE
Laxative	Constipation	Stimulant: e.g. Senna 7.5mg/5ml, age 2-6yrs 2.5-5ml/day, age 6yrs+ 5-10ml/day.
Tricyclic antidepressant	Neuropathic pain (especially burning)	Amitriptyline, 0.2-0.5mg/kg nocte, increasing by 25% every 2-3 days if necessary up to antidepressant levels.
Anticonvulsant	Neuropathic pain (especially shooting or stabbing)	Phenytoin,2.5-5mg/kg bd
Neuroleptics	Nausea, confusion, psychosis	Haloperidol, 0.01-0.1mg/kg tds

MEDICATION	INDICATION	DOSAGE
Sedatives	Acute anxiety, muscle spasm, premedication.	Diazepam, 0.05-0.1mg/kg qds
Corticosteroids	Raised intracranial pressure, spinal or nerve pressure, and others.	Dosage depends on clinical situation

SUPPORTING PATIENT AND FAMILY DURING TREATMENT:

Continuity of care - communication is essential between pharmacists and the prescribers so all are aware of changes and so that the patient and family are not confused by any alterations to medication made,

Each patient is different. Patients know their own bodies better than their doctors and must be listened to if medications do not suit them and suitable alternatives found. Remember that the body metabolism rate is changing as the body deteriorates. Deterioration in renal function is usually the first to be recognised. Drugs take longer to be excreted leading to build up of metabolites. In the case of morphine the patient now will become sleepy and this indicates that the dose must be reduced, or the time interval between each dose should be lengthened.

1.16 MEDICATION IN THE DYING PATIENT:

One of the biggest barriers to good care of the dying is healthcare professionals' reluctance to diagnose dying. Recognising the key signs and symptoms is an important clinical skill. Thus patients suffer unnecessary investigations and extraordinary treatments which are unnecessary and contribute to a most painful death. *Health professionals need to look ethically at such situations. Not only must we refuse to carry out such procedures ourselves, but also support our colleagues in withdrawing from such treatments.*

In cancer patients, usually death is preceded by a gradual deterioration in functional status:

The patient may become bed bound.

The patient may be semi-comatose.

Urine output reduces

Patient is very weak

Patients does not want to eat or drink

Remember that parenteral fluids are contraindicated at this time. Fluids given parenterally build up in the body causing oedema including swelling of the brain. Pain can then worsen. Fluids also collect in the stomach and vomiting occurs with aspiration because of the weak cough reflex.

Patient should be allowed to rest. Food and drink should only be given on request by the

patient. The mouth should be kept moist with dripped in water as dry mouth is the most uncomfortable part to the patient.

Relatives need to have been prepared for this and the reason for not forcing food and fluid explained. The comfort of the patient is paramount at this time so that family and patient may heal and make their peace with each other and with God.

A peaceful death, with the family working closely with an understanding health professional, brings peace to the family, through fond memories of the loved one.

1.17 PAIN CONTROL: CHECK LIST AND SUMMARY

1. HOLISTIC ASSESSMENT: including psychological, spiritual, cultural and social aspects.

2. ACCURATE DIAGNOSIS of cause of pain: defined as somatic or neuropathic.

3. ANALGESICS –

   A: Analgesic ladder (WHO).

   B: Neuropathic analgesia.

4. ADJUVANT DRUGS (co-analgesics) used appropriately.

5. Consider:

   i) RADIOTHERAPY.

ii) HORMONE THERAPY.

iii) CYTOTOXIC CHEMOTHERAPY.

iv) Surgical/ ORTHOPAEDIC PROCEDURES.

v) NEUROLYTIC PROCEDURES. *

6) TRANSCUTANEOUS NERVE STIMULATOR, ACUPUNCTURE.

7) ALTERNATIVE THERAPY EG AROMATHERAPY, MASSAGE, TRADITIONAL THERAPY: check it out if it is helping or not.

8) NEUROSURGICAL PROCEDURES.** (Not yet available in Uganda).

SECTION II:

THE CONTROL OF OTHER SYMPTOMS IN CANCER AND/OR AIDS PATIENT

SECTION II: THE CONTROL OF OTHER SYMPTOMS IN CANCER AND/OR AIDS PATIENT

People living with HIV and cancer experience multiple symptoms and complaints which cause much suffering. Helping to improve or prevent these symptoms often restores good quality of life and allows people to enjoy normal living. It is a vital part of providing good palliative care and support. Treating symptoms effectively also helps patients living with HIV to adhere to their ARVs.

Symptoms may be caused by:

- Illness itself (e.g. pain due to cancer or weight loss due to HIV)
- Infections (e.g. cough due to TB, or headache due to cryptococal meningitis)
- Treatments/ medications e.g. constipation due to morphine, visual problems due to anti-TB drugs.

In an African study among 103 patients with stage IV AIDS (most of whom were not receiving ARVs), the most common symptoms were:

- Pain (98%),
- Weight loss (81%),
- Loss of appetite (70.9%),
- Low mood (69.9%),
- Weakness (66%),
- Dry skin (56.3%),
- Diarrhoea (53.4%),
- Nausea and vomiting (44.7%),
- Cough (44.7%)
- Fatigue (42.7%).

2.1 RESPIRATORY AND THORACIC SYMPTOMS:

COUGH

Cough is most commonly seen in patients with lung cancer, tuberculosis and the pneumonias with AIDS. Among patients living with HIV/AIDS, cough persisting for more than 2-3 weeks should be considered suspicious for TB, and patients referred for investigation/ treatment if available. In general, unless the underlying cause can be removed, there are few truly effective measures to relieve symptoms entirely, though a variety of measures may be considered

CAUSES:

1. Bronchial obstruction from a primary tumour or mediastinal mass, most commonly enlarged mediastinal glands.
2. Tuberculosis or pneumonia in immuno-suppressed patient.
3. Secondary bronchial infection, tuberculosis, pneumonia or an abscess in a necrotic tumour.
4. Left ventricular failure with characteristic dyspnoea and cough wakening the patient.
5. Vocal cord paralysis due to hilar tumour or lymphadenopathy.

MANAGEMENT

If available consider radiotherapy or chemotherapy for obstructing tumour.

Patients with a productive cough are seldom as disturbed as are those with a dry irritating cough caused by a bronchogenic carcinoma, mediastinal obstruction.

❖ PRODUCTIVE COUGH:

a) Postural drainage can aid expectoration and drainage if the condition of the patient can take it. Nurses must be experts in this. Rarely a physiotherapist is available but the family can be shown simple techniques within the range of comfort for the patient. Help can be found in useful booklet "Where there is no physiotherapist" by Anne Aslett, 2011, Hospice Africa Uganda publication.

b) Antibiotics are often useful in clearing infection and facilitating easier expectoration. They should always be considered in the AIDS patient. Unscientific as it may appear they are occasionally useful even when no pathogens have been demonstrated in sputum cultures. (Remember C&S may not always be accurate and sensitivities may be according to the pellets available from the manufacturing company. Avoid unless clinical knowledge not able to provide the diagnosis.

c) Mucolytics: may appear to be useful in spite of the paucity of scientific data to support their use, but only when used regularly for a minimum of four weeks. Keep prognosis in mind.

d) If bronchospasm is present a bronchodilator in or out of cough mixture is helpful e.g.. Ventolin (salbutamol) or cough linctus.

- **DRY COUGH:**

Is undoubtedly helped by:

a) COUGH SUPPRESSANTS, for example:

- Codeine linctus (1mg/ml 10ml 4-hourly) or codeine tabs 30mgs 4 hrly.
- Morphine solution (2.5mg 4-hourly).

For cough suppression the dose of morphine used is the lowest needed to alleviate this symptom. b) HUMIDIFYING OF THE ATMOSPHERE with steam can be done in the home using a kettle or a basin of hot water breathed in under a towel.

c) STEROIDS (dexamethasone 2mg/day) may be used in cancer patients to reduce oedema surrounding a tumour, relieve bronchial oedema and lessen bronchospasm. They are also needed in lymphangitis and radiation pneumonitis, which also cause cough.

Limit to a short course if the patient is suspected of having AIDS and include an antifungal.

d) Local anaesthetic lozenges if available can be useful in laryngeal/tracheal irritation and patient should not eat or drink for an hour after taking.

NURSING TECHNIQUES

Much confusion appears to exist about the most appropriate nursing techniques. The

rules are simple.

a) If the cough is secondary to an uncomplicated bronchogenic carcinoma the patient is seldom comfortable propped bolt upright in bed but better nursed with only two or three pillows. The key is the position most comfortable to the patient. Failure to do this may further embarrass respiration.

b) If due to chronic bronchitis and obstructive airways disease he should be asked to sit up or propped up as straight as is comfortable.

c) In pneumonia, the patient is usually more comfortable resting, with two pillows, but always give way to the position most comfortable for the patient.

d) If there is a pleural effusion (whether necessitating aspiration or not), he should lie on the side of the effusion in a semi-recumbent position. Pleural aspiration is often a painful procedure and the doctor must not only be prepared to prescribe appropriate analgesics but remember the problems of nursing a patient on the side of aspiration. We have found a combination of frusemide and spironolactone useful in delaying the necessity for aspiration if there is an element of heart failure. Watch patient's hydration if combination of diuretics is commenced as there is a risk of dehydration. Do not persist if excessive dryness of mouth results.

DYSPNOEA

Dyspnoea is a subjective experience of difficult, laboured, and uncomfortable breathing.

In recent studies, breathlessness was reported in the final week of life in 69% patients with lung cancer or lung metastases and in 91% of patients with chronic lung disease (Western assessment),

and in 66% of hospitalised patients dying from cardiac failure in final 24-72 hrs.

It is one of the most feared symptoms because all such patients anticipate death from suffocation and asphyxia. An explanation that the mode of death is more likely to be increasing drowsiness leading to coma is sometimes helpful, and reassurance that all symptoms will be addressed including breathlessness.

No effort should be spared in attacking this symptom and finding all means to relieve the patient's anxiety, which often borders on panic.

Cause of breathlessness should be considered and treated if possible particularly in patients with HIV/ in early stage disease. Having said this, it must be recognised that very little can be done for the underlying pathology in obstructive airways disease, bronchial obstruction by tumour or lymphangitis carcinomatosis at the end-stages of disease. If patient is still conscious and

aware of symptoms, low dose opioids and benzodiazepines, along with calm and reassurance, can be very helpful in lessening distress. It is also vital to provide reassurance to the family who stay by the bedside.

CAUSES OF DYSPNOEA:

1. CAUSED BY CANCER AND/OR AIDS: Effusion, atelectasis, consolidation, massive ascites, replacement by cancer (KS), lymphangitis of functioning lung

2. RELATED TO TREATMENT:Post-radiation fibrosis, post-pneumonectomy

3. RELATED TO DEBILITY: Anaemia, pneumonia, pulmonary embolism, CMV

4. UNRELATED TO CANCER OR TREATMENT: chronic obstructive airway disease or asthma.

MANAGEMENT:

(a) Attempt to modify the pathological process e.g. with anti-pyretics, cortico-steroids, (care in AIDS) radiation therapy, hormone therapy, chemotherapy, pleural aspiration when appropriate.

(b) Use such non drug measures as a calming presence, cool draught from an open window or fan, breathing exercises, relaxation therapy.

(c) Anxiolytics such as oral diazepam 2 -10mg each night for sustained effect, or triazolam 0.0625-0.125mgs (shorter acting

benzodiazapine if available) to enable sleep during the most alarming time of the day.

(d) Equally effective in reducing sensation of breathlessness by a number of mechanisms, is low-dose morphine regularly, e.g. morphine solution

2.5 - 5mg every 4 hours or MST 10mg 12 hourly. If already using high dose morphine for pain, increase by 1/3 of total dose or in weaker patients, 2.5mg 4 hrly increments until dyspnoea controlled.

(e) Suppress paroxysmal cough exacerbating dyspnoea with morphine or codeine linctus and hot drinks.

(f) Panic attacks are best treated with oral or rectal diazepam (5 - 20mg). Oral or rectal routes act more quickly than i.v., because of the metabolism of diazepam. Rectal diazepam preparations are very expensive. However diazepam for injection can be inserted into the rectum using a syringe (minus the needle!) and is equally as effective and usually more available.

Oxygen is necessary only for the same indications as at any other time in medical practice; contrary to what some patients and many relatives may feel, it has been not shown to be effective in treating dyspnoea/ breathlessness in non-hypoxic patients. Oxygen is often not available in the African situation and fanning with the local newspaper often gives just as much relief.

The doctor has a responsibility to explain carefully that oxygen will not prolong the life of the patient with lung cancer, nor resuscitate a dying patient.

No medication replaces this reassurance.

Specific causes of DYSPNOEA

PLEURAL EFFUSION

Though not strictly a symptom, this complication is common enough to pose a problem to the clinician. The rule is that it should be aspirated only:

(a) For diagnostic purposes

(b) If, by so doing, incapacitating dyspnoea will be relieved.

Where the effusion is likely to recur and the life expectancy of the patient is still likely to be long, it is worth considering the instillation into the pleural space of an agent producing pleurodesis. Eg. Bleomycin or tetracycline powder. Tapping of effusions has been shown to increase the rate of fluid accumulation and the tapping needs to be repeated at shorter and shorter intervals.

Some patients with effusions due to cardiac failure, respond to frusemide 40 mgs with spironolactone 50– 100mgs daily, and it is worth trying to delay the inevitability of aspiration.

Although malignant effusions do not physiologically respond to diuretics, they

have responded in our experience here in Uganda. The dose has to be monitored and reduced in the light of side effects.

It is worth remembering that pleural effusion secondary to a bronchogenic carcinoma or adenocarcinoma of the lung, carry a poor prognosis. On the other hand, patients with breast carcinoma complicated by pleural effusion may still survive many months.

SUPERIOR VENA CAVA OBSTRUCTION

Superior vena cava obstruction merits attention because of the extreme distress it can produce and its response to therapy. Lung cancer is responsible for majority of cases. Other causative tumours include lymphoma, breast cancer and seminoma. Every patient with a bronchogenic carcinoma, neck tumours or known mediastinal spread from any tumour should regularly be examined for the earliest signs of its development.

Clinical features include:

- Breathlessness
- Neck and facial swelling
- Trunk and arm swelling
- A sensation of choking
- Headache
- Neck vein distension
- Plethora

Occasionally it may present as one of the emergencies of terminal care.

MANAGEMENT

(a) Steroids: eg dexamethasone
- 24mg stat iv or p.o. 1st day
- 12mg 2nd day.
- Maintenance: 4-8mg per day in divided doses.

(b) Consider PROMPT RADIOTHERAPY, or cytotoxic chemotherapy (depending on the tumour histology) but often not available to our patients in Uganda and African countries.

Remember that a patient on radiotherapy may have this complication due to oedematous reaction around the tumour.

Stop radiotherapy and treat as above. This is a rare radiotherapy (RT) reaction.

HAEMOPTYSIS

This may occur as an early or initial event in the lung cancer journey or as a terminal event. It may also occur in TB. Mild haemoptysis can be coped with early on and the patient reviewed and treated for infection if appropriate, referred for RT in patients where cause is due to lung tumour. Hospitalisation may also be indicated if blood transfusion is available and still appropriate. If available tranexamic acid 1g TDS can be helpful for mild bleeding.

However catastrophic haemoptysis is alarming to both patient and family. The families need to be prepared if this is a possibility so that they do not start rushing to hospital in the terminal stages.

MANAGEMENT:

If patient able to swallow give double usual dose of morphine +/- diazepam. This sedates the patient and relieves the panic. Calming presence of carer/relative who has been prepared and told not to appear to panic in front of the patient and can express this to visiting relatives. Keep free of blood using receptacle and changing materials soiled with blood. Dark coloured cottons should be used in preference to white or pastel shades when the colour red alarms the patient.

STRIDOR

This is an unusual complication in our experience but can be most distressing to the patient the family. Again morphine orally and benzodiazepine e.g. diazepam can relax the patient. Explanation needs to be given to the patient and family. High dose steroid can help if it is due to tumour compression. If there is a response to steroids and patient well enough, consider palliative RT where available.

2.2 HICCUP

MANAGEMENT

CAUSES OF HICCUP

1. IRRITATION OF THE PHRENIC NERVE by tumour involvement at the hilum of the lung.
2. DIRECT IRRITATION OF THE DIAPHRAGM (infection, tumour).
3. URAEMIA.
4. DYSPEPSIA (especially with hiatus hernia).
5. ELEVATION OF DIAPHRAGM (from enlargement of the liver or ascites).
6. CNS tumour

Immediate:

(a) Pharyngeal stimulation e.g. by swallowing dry bread or two teaspoons of sugar.

(b) Correct uraemia if possible.

(c) Simple re-breathing from a paper bag to elevate pCO2 level.

(d) Drugs:

(i) Haloperidol 0.5mg bd orally or 1.5mg intramuscularly during attacks.

(ii) Chlorpromazine 12.5- 25mg bd. or prn during attacks (although its sedative effect may distress the patient).

(iii) Metoclopramide 10mg qid or domperidone 10-20mg qid, may be quite effective if due to gastric distension.

(iv) Muscle relaxants e.g. baclofen 5-10mgs TDS are effective for some patients

2.3 THE 'DEATH RATTLE'

Noisy breathing due to the accumulation of secretions in the large airways, in the patient whose conscious level is falling prior to death, is often more distressing to those around than to the patient. This should be explained, particularly to relatives. Position should be changed regularly to prevent pooling of secretions.

MANAGEMENT

(a) Position of the patient is important THE HEAD SHOULD BE LOW ensuring that

secretions can drain from the mouth.

(b) Hyoscine butyl bromide (Buscopan) 10-20mgs subcutaneously helps reduce the production of secretions. But must be given early and regularly to be effective as it does not clear secretions already there.

(c) Morphine subcutaneously may be given along with the hyoscine, if the patient is too ill to swallow. (The dose will depend on the dosage of morphine the patient has been having previously.) This is very important if the patient is still semi-conscious to relieve breathlessness.

3. INTESTINAL SYMPTOMS

3.1 ANOREXIA:

Refers to reduced appetite or lack of desire for food and is a common symptom in HIV and in many cancers. In the earlier stages of disease it is important to try to establish cause and to reverse if possible. E.g. Causes include:

Painful mouth due to ulcers/Candida/tumour, nausea or vomiting, underlying cancer (may be associated with significant with significant weight loss), "squashed stomach syndrome" due to enlarged liver, chronic pain, constipation, depression.

In the dying phase however, it is more appropriate to treat food as a comfort issue and to offer small amounts of what the patient wishes to eat. It is extremely important to reassure family that forcing extra food at this time would not prolong patient's survival but cause discomfort.

Treatment

1. Treat reversible causes e.g. oral candida, anti-emetics for nausea, laxatives for constipation, analgesia for pain, counselling and/or anti-depressants for depressed mood.

2. Non-drug measures

- Offer small portions of food regularly rather than large platefuls, and

- Remember patients can eat more sitting up with the family or sitting beside the bed.
- Avoid strong odours that may cause nausea.
- Do not pressurise the patient. Tempt the patient with minute helpings of favourite foods on the smallest plate available.
- Offer attractively served food at frequent intervals unrelated to standard meal times.
- Offer a small alcoholic drink of choice if interested (Not common among our sick in Uganda).
- Be reluctant to offer 'invalid' food no matter how nutritious, but ever ready to permit and encourage any bizarre fancy the patient may have even if it is not considered suitable for an Invalid e.g. cassava crisps, matoke at breakfast, coke.

3. Drug treatment

Steroids e.g. prednisolone 15-30mg daily reducing to 15mgs daily or dexamethasone 4mgs mane reducing to 2mg/day have been shown to improve appetite transiently (period of 2 –3 weeks) in cancer patients in a number of trials. They may also improve energy and sense of well being. However they need to be used with caution and for short periods only in patients with HIV.

Steroids are the only 'tonic' recognised as

having any efficacy in promoting appetite. Other steroids like megestrol acetate are used in developed countries but neither available nor affordable in the usual African setting.

Causes of anorexia:

- Oral thrush (present in 75% of patients),
- Chronic constipation
- Uninteresting, unimaginative food
- Too large helpings, or food offered only at standard meal times
- Odours in environment
- Nausea and vomiting
- Secretion of anorexant substance by the tumour
- Squashed stomach syndrome (see below)
- Excessive medication and/or dry mouth (itself often drug-induced)
- Depressive state
- Metabolic- hypercalcaemia, uraemia

3.2 SQUASHED STOMACH SYNDROME

This condition is relatively common in Africa. It occurs when tumour mass, enlarged liver or large volume ascites squash the stomach, reducing the volume so that the patient feels full and satiated after a small amount of food. Common causes are liver enlargement, ascites and tumours arising from the pelvis such as ovarian cancer or bowel involvement.

Other symptoms are oesophageal regurgitation, heartburn and constant fullness.

MANAGEMENT:

1. Frequent small meals.

2. Increase volume of the stomach by removing some gas, ie give antacid.

3. Control nausea and increase gastric emptying with metoclopramide 10 mgs tds, half an hour before meals for a short period.

4. Decrease space occupying cause eg for tumour try corticosteroids, for ascites try frusemide 40 – 120mgs with spironolactone 50 – 100mgs daily.

5. Patients should be advised to sit up and wait 30-60minutes after their meal before going to sleep at night.

3.3 SORE MOUTH

Patients with HIV/AIDS or cancer are prone to mouth problems. These can make eating, drinking and swallowing very painful, and impair quality of life.

Simple oral hygiene and some basic medications can help prevent opportunistic infections and mouth sores.

Mouth care can be maintained by careful and gentle cleaning of teeth and gums. Remove bits of food stuck in the mouth with cotton wool, gauze or soft cloth soaked in salt water. Rinse the mouth with diluted salt water (a pinch of salt or soda bicarbonate in a glass

of water)

Anything, which makes eating, or swallowing difficult is worth treating as much for the sake of relatives, who feel that feeding the patient is a way of showing they care.

CAUSES OF SORE MOUTH

1. Oral candidiasis, present in 75% of patients but often missed because it may present as a spongy red mucosa (with angular stomatitis) or because failure to look at the mouth for the classical white curds. In AIDS patients the team must be particularly vigilant for this.
2. Oral ulceration associated with AIDS or occasionally aphthous ulcers.
3. Cytotoxic therapy: in some cases a marked stomatitis may occur.

MANAGEMENT

Generally keep mouth fresh by rinsing with a saline solution made up of a pinch of rock salt in a mug of water.

(a) For candidiasis:

(1) Nystatin (100,000IU/ml) 5ml after meals and at night.

Patient should be instructed to hold or rinse around the mouth as it acts topically.

(2) Nystatin lozenges 500,000 after meals and at night

(3) Fluconazole 100-200 mgs daily for 7-14 days or ketoconazole 200

mg daily. Note ketoconazole is an enzyme inhibitor and therefore causes potential drug interactions with ARVS.

(b) Mouth ulcers respond to crushed prednisolone tabs with a small amount of powder applied topically.

(c) Occasionally, even in the absence of proven infection, post chemotherapy stomatitis improves with co-trimoxazole suspension in the usual dose regime. *Given time, it will clear spontaneously.*

(d) Foods are usually preferred either icy cold or very hot. Semi solids are preferred to either fluids or solids. Give soft, mashed food, avoid acidic drinks e.g. fruit juice/ soda. Use cold water/milk instead

(e) 1% aqueous Gentian violet applied hourly gives good results.

3.4 HALITOSIS

This is seldom reported, but often suffered. Patients are often not aware of it and it goes without saying that it is a source of great distress and embarrassment to relatives.

CAUSES

1. Bad oral hygiene (thrush, dental sepsis, dentures, loss of saliva, mouth breathing, dehydration).

2. Cesspool halitosis because of delayed gastric emptying or a gastric carcinoma (particularly linitis plastica) or an oesophagus dilated by a distal stricture.

3. Carcinomas of mouth e.g. Kaposi's sarcoma, larynx, pharynx and bronchus.

4. Sinus and naso-pharyngeal infections.

5. Pre-existing bronchiectasis.

6. Cancrum oris.

MANAGEMENT

(a) Energetic attention to oral hygiene in all patients.

(b) Use of mouthwash made up with metronidazole tabs crushed or metronidazole liquid for injection, with fruit juice of the patients choice. It can be used as a gargle or as a mouthwash or even swallowed.

(c) Metoclopramide 10mg qid, to speed gastric emptying.

(d) Sucking of favourite "sharp" food or fruit e.g.. pineapple, (contains proteolytic enzyme "ananase") passion fruit, orange or lemon.

(e) The odour from a bronchogenic carcinoma may be reduced by metronidazole 200mg tid by mouth or by gargle which is then swallowed.

(f) Keep mouth moist with water drips, or ice chips if available. Keep lips from cracking with petroleum jelly.

3.5 DYSPHAGIA

This means difficulty swallowing and may occur in HIV/AIDS or cancer. It has significant impact on quality of life. Patients are usually disappointed that they can swallow very little food but frightened beyond words at the possibility of choking to death or inhaling regurgitated food.

CAUSES

1. Pharyngeal obstruction (e.g. due to lymphadenopathy/tumour, extrinsic pressure).

2. Oesophageal candidiasis and/or ulceration (common in AIDS).

3. Oesophageal obstruction (commonest cause in Uganda).

4. Intrinsic from carcinoma, blocked Celestin or Atkinson tube

5. Extrinsic from enlarged mediastinal glands and tumours of the neck.

6. Specific neurological disorder (such as motor neuron disease, cancer or HIV invasion of nerves).

MANAGEMENT

(a) Always be suspicious of candidiasis, which may develop very rapidly even in the patient taking nystatin oral suspension, particularly if taking steroids or antibiotics. Fluconazole 100-200mgs tab

daily x 2 weeks may be prescribed along with nystatin if the candida infection is particularly troublesome. Many AIDS patients have taken different antifungals and are resistant. Try clotrimazole 500mgs pesssaries (put in jar marked lozenges!), given as a lozenge to suck once daily for 5 days. This has been life saving in our experience.

(b) If due to tumour, try and reduce tumour bulk or inflammation by dexamethasone 16 mgs, reducing slowly. If not swallowing by the third day, stop. This sometimes gives a period of being able to swallow in the debilitated patient. ALWAYS give concurrent anti-fungal. If available, consider referral for radiotherapy to reduce tumour mass (effect likely to depend on how radiosensitive tumour is, but has been helpful for head and neck and oesophageal cancers).

(c) For oesophageal obstruction, if available, a Celestin or Atkinson Tube or stent can prolong life. Thereafter soft, pounded foods can be taken easily. A feed of soda or 1 teaspoon of honey in warm water can keep the tube clear. The same procedure is repeated after each meal.

(d) In complete obstruction and where prognosis is such that patient is likely to survive for some time, and if patient is hungry, gastrostomy (feeding tube placed into stomach from outside) may even be considered to prolong life and

improve quality of life. If prognosis is very short and patient has no desire for food then it is unlikely to be of any real benefit to the person. All of these factors should be considered and *discussed with patient and family* if such a procedure is being considered. The ethics of such procedures are in question if the patient and family are not fully informed of the problems and prognosis before such procedures are carried out.

(e) DEXAMETHASONE (initially 8-12mg/day) for mediastinal obstruction not amenable to radiotherapy or chemotherapy.

(f) Show family or carer adequate oral hygiene and hydration and correct positioning, ie sitting upright for at least ½ hr after meals.

3.6 NAUSEA AND VOMITING

Upsetting as it is, vomiting is less distressing to many patients than persistent nausea, and sometimes easier to control. Neither symptom is an inevitable feature of terminal illness. Though nausea may not always be accompanied by vomiting the two symptoms are best considered together.

Nausea associated with cancer and HIV disease is often multifactorial. Often, a specific cause or causes cannot be identified. However treating nausea is vital, as it can make life miserable, interfere with ARV adherence and result in malnutrition.

Causes

1. GI causes- opportunistic infections, reflux, gastritis, constipation, GI malignancy, intestinal obstruction, liver disease, pancreatic problems (GI infections should be ruled out in patients at risk for opportunistic illnesses (CD4 <200 cells/ µL). Oesophageal reflux is common in patients with advanced HIV disease).
2. Medications-ARVS especially protease inhibitors, antibiotics, NSAIDS, chemotherapy. *It cannot* be emphasized enough that opioids seldom cause persistent nausea after four or five days of regular use. This initial vomiting is extremely rare in African patients.
3. CNS causes- CNS Opportunistic infections and malignancies
4. Anxiety
5. "Chemical"/toxins e.g. hypercalcaemia, uraemia, septicaemia
6. Others e.g. cough

MANAGEMENT

1. **Correct causes/exacerbating factors where possible**:

- GI infection- treat
- Gastritis- H2 antagonist e.g. ranitidine or proton pump inhibitor e.g. omeprazole 20mg OD
- Consider stopping gastric irritant drugs e.g. NSAIDS

- Constipation- Use laxatives
- Raised intra-cranial pressure due to tumour- Use dexamethasone and consider radiotherapy (Note steroids unhelpful in cryptococcal meningitis)
- Anxiety- listening + reassurance. Diazepam in low dose if severe/ persistent.
- Cough- Treat cause. Use anti-tussive e.g. codeine/ low dose morphine
- Hypercalcaemia-Treat if drugs available.

2. Non-Drug measures:

Avoid strong smells if possible

Manipulate diet, the temperature of the food and timing of meals. Use small portions

3. Introduce antiemetic:

Prescribe the most appropriate (available) anti-emetic regularly. If actually vomiting use s.c. or rectal route. (In some countries continuous subcutaneous pumps are available and may be considered if persistent vomiting). Certain anti-emetics may be administrated using a subcutaneous pump e.g.. Haloperidol 2.5 - 5mgs per 24 hours, metoclopramide 30-60mgs per 24 hours

anti-emetics (depending on desired site of action).	
CENTRAL ACTION:	G.I. TRACT
*prochlorperazine	**metoclopramide****
*chlorpromazine	domperidone
*promethazine	**cimetidine*
*haloperidol	*ranitidine*
cyclizine	
*hyoscine	

***presently available in Uganda*.**
****Also have central action**

- For gastritis, gastric stasis, regurgitation, functional bowel obstruction use a pro-kinetic anti-emetic- e.g. metoclopramide 10 mg QDS or domperidone 10-20mg TDS
- *For most chemical causes of vomiting e.g. drug-induced, renal failure, bacterial toxins use a* centrally acting (brain) anti-emetic (mainly in chemo-receptor trigger zone) e.g. haloperidol 1.5-3mg at night/BD, metoclopramide also has central action.
- *If bowel colic and/or need to reduce GI secretions e.g. bowel obstruction due to GI malignancy* use anti-spasmodic or anti-secretory anti-emetic- Hyoscine butylbromide 20 mg stat s.c. + TDS

- *For raised intra-cranial pressure (in conjunction with dexamethasone for tumours), motion sickness use an a*nti-emetic acting mainly in vomiting centre- e.g. cyclizine 50 mg TDS (if available), or haloperidol.
- *For intractable nausea and vomiting if combining above classes does not control :*Broad-spectrum anti-emetic e.g. levomepromazine, if available, 3-6 mg PO or 12.5 mg SC at bedtime/ BD. If unavailable, trial chlorpromazine 12.5 mg BD. Both drugs are sedating.
- Other antiemetics that occasionally help if cause is unclear, are dexamethasone (usual caution in immuno-suppressed), ondansetron (in chemotherapy-induced nausea but extremely expensive and causes constipation).

It should be remembered that terminally ill patients seldom like the sedative effects of centrally acting anti-emetics, and that in a few patients two anti- emetics will be required (one centrally acting, one gut acting).

3.7 CONSTIPATION

Many patients seen by palliative care teams in hospitals and the communities are found to be very constipated. Although often considered unimportant, it is a common cause of vomiting in the terminally ill, a common cause of unnecessary abdominal discomfort, anorexia, and confusion/ delirium. It is a source of considerable anxiety to many

patients, particularly the elderly, who see it as further evidence of breakdown in their body's basic functions. Professional reassurance that it is not serious or life-threatening does not help. It is usually possible both to prevent it and correct it.

CAUSES

1. Impaired fluid intake or excessive loss through vomiting, tachypnoea, or sweating.

2. Small food intakes of predominantly low roughage, high milk content diet ('invalid foods').

3. Relative immobility/weakness particularly associated with breathlessness in lung cancer, paraplegia.

4. Drug-induced (opioids, cough sedatives, anticholinergic drugs, tricyclic anti-depressants, phenothiazines, diuretics etc.)

PREVENTION AND MANAGEMENT

The normal regime of encouraging a diet of high fibre, fruit and fluids is not usually appropriate in a patient, as they are seldom able to take them. Laxatives are required and the patient encouraged to have a reasonable fluid intake.

RECTAL EXAMINATION - *It cannot be stressed strongly enough that rectal examination should be carried out, with the patients*

consent, during initial examination for most patients. Exceptions include patients whose condition is very weak, or when further bleeding or pain would be caused by the procedure.

(a) When the rectum is found to be filled with hard faecal masses do NOT give any faecal expander, eg fibre like psyllium or methylcellulose, which will only convert a small hard mass into a large soft one, impossible to expel in debilitated patients who already have reduced fluid intake.

Manual removals are required and may have to be continued until death. Families can usually be shown how to do this (see below). If unsure call the Hospice nurse for advice.

(b) When the rectum is empty but ballooned, indicating faecal impaction around the recto sigmoid junction, do not give a faecal expander alone without a peristaltic stimulant, nor use suppositories. The only effective treatment is a "softener" accompanied by a "pusher" e.g. a tablespoon of margarine (Blue Band) or vegetable oil, given before breakfast can assist a hard mass to slip out, together with senna or bisacodyl . Regualar rectal examinations should be carried out to detect the descent of the mass into the lower rectum. Manual removal or phosphate (or soap and water) enemas are then indicated.

(c) When the rectum is empty but collapsed, there is no faecal impaction. Oral faecal expanders and/or peristaltic stimulants will be effective.

(d) Consider using local herbal laxatives or foods, which the patient has found useful previously. E.g. Crushed papaya seeds, coffee from the coffee senna tree.

Above all, remember that each patient will have different needs. Assessment of the situation includes listening to relatives on a day to day basis, and changing regimes to suit changing needs.

PREVENTION WHEN USING OPIOIDS

All patients prescribed an opioid (ladder step 2: codeine, or ladder step 3: morphine,) must simultaneously be prescribed laxatives, whether previously constipated or not. The exception to this is the AIDS patient with chronic diarrhoea, when he will bless you for relief!!

Typical MAINTENANCE regime is:

Bisacodyl or senna tabs: 2-5 tablets at night, starting with 2 tablets and increasing nightly until having a motion the next morning. Dried*crushed* paw paw seeds can also be used, 1 to five teaspoons at night. Crushing them is important as the active ingredient is inside the seeds. Otherwise the seeds pass through

without any action on the constipation. Then reduce to a level where the stool is as normal as possible for the patient. This may need to be followed by bisacodyl suppository with or without glycerine suppository (or a plug of petroleum jelly)) the following morning after breakfast if the patient is very weak. Again a tablespoon of margarine can assist. Some patients prefer a traditional herbal laxative that they have used previously with success. Encourage high fluid intake.

In the absence of suppositories, insert a lump of petroleum jelly (Vaseline or "Bright Light") into the rectum and ask the patient to try and hold it for 20 minutes before passing stool.

***MANAGEMENT OF ESTABLISHED CONSTIPATION*:**

MANUAL REMOVAL

Manual removal of hard faeces gives immediate relief of tenesmus.

1. Explain to patient the procedure
2. Prepare newspaper or other receptacle to receive the faeces removed.
3. Put a rubber glove on right hand and apply KY jelly to 1st finger.
4. Stroke outside of anus to relax the sphincter, then gently insert finger, stopping if spasm occurs giving time for muscles to relax.
5. Remove small pieces of faeces piece by

piece. Break up large pieces with finger before removal.

6. NOTE: Avoid oil containing laxative such as "Agarol" orliquid paraffin as they can cause aspiration pneumonia in debilitated patients, malabsorption of fat soluble vitamins and uncomfortable leaking around anus when used on a regular basis.

7. Talk to patient throughout procedure, asking him to take deep breaths in order to relax. If pain or discomfort is too much, finish and continue another day. This procedure may need to be repeated alternate mornings by nurse or by relative, who can be shown the procedure. Once the "plug" has been removed a laxative at night can be commenced. Some patients need this regime until death because they never regain sufficient strength to expel faeces. Patients with neurological difficulties such as paraplegia will need manual removals on a regular basis.

Avoid bed pans as passing motion sitting with legs out- stretched, does not aid abdominal muscle contraction. Allow patient to squat or sit out if possible.

3.8 DIARRHOEA

Though relatively rare in cancer patients, diarrhoea occurs in over 50% of people with HIV/AIDS. *(*In cancer patients, one of the commonest causes is constipation causing

"overflow diarrhoea".) *AIDS-related diarrhoea can produce up to 20 stools per day with severe dehydration.*

In HIV/AIDS patients, infectious causes of diarrhoea should always be out ruled, or treated empirically if patient too unwell for investigations. Diarrhoea due to HIV itself or HIV enteropathy may be the cause in advanced disease. Chronic intermittent diarrhoea is relatively common in patients with stable HIV disease. This may be related to medications (antiretrovirals especially protease inhibitors) or idiopathic.

Assessment: "Diarrhoea" can mean different things to different people - a single episode of loose stool, more frequent bowel motions than usual etc.

Therefore it is important to be specific. Ask about consistency of stool, frequency and urgency of bowel motions, presence of blood or mucus. For many patients it is the urgency rather than the volume or frequency of bowel movements that is most distressing. Incontinence can be hugely upsetting and restrictive for people.

MANAGEMENT

1. Treat causes if possible.

In cancer patients, rule out faecal impaction by abdominal and rectal examination. Treat infection if present in HIV patients. Stop causative drugs e.g. antibiotics, where

possible. ARV-associated diarrhoea may respond to switching drugs (if this is an option).

1. Ensure hydration maintained with ORS or in severe dehydration, IV fluids.

   Use oral dehydration salts (ORS) initially. These can be made up in the home with 1 tsp salt and 2 tsp sugar dissolved in 1 litre boiled water. Flat coca cola can also be used. Give these a try before commencing medications.

2. Drug Treatment
   - Patients with chronic diarrhoea benefit from anti-diarrhoeals taken after a loose motion or from 1 to 4 times per day e.g. loperamide 2-4mg
   - Antispasmodic medications e.g. hyoscine butylbromide 20 mg QDS decrease motility, whereas fibre improves stool consistency. Patients with mixed constipation alternating with diarrhoea may be treated with daily fibre and PRN antispasmodics.
   - Low dose morphine e.g. 2.5 mg TDS, titrating to effect, or other opioids e.g. codeine phosphate can be helpful if other measures, and are usually well-tolerated.
   - *If vomiting, morphine may be dripped into the mouth and be absorbed from the buccal mucosa.*

3. Nursing care: keep dry using waterproof plastic under sheet covered with cotton sheet or absorbent material, counsel attendants.

3.9 FAECAL INCONTINENCE

This is obviously a distressing symptom for the patient, and a difficult problem for his/her relatives to cope with at home.

CAUSES

1. Excessive and frequent diarrhoea in the debilitated patient.
2. Paraplegia.
3. Lax anal sphincter, particularly in the elderly.
4. Faecal impaction producing spurious diarrhoea.
5. Ano-rectal carcinoma.
6. Excess intake of laxatives.

MANAGEMENT

It is important to do a thorough rectal examination to define the cause. The patient with a lax sphincter may benefit from a constipating agent (e.g. loperamide, codeine phosphate), the paraplegic and/or constipated patient from appropriate rectal evacuation and regular faecal expanders (softeners). The patient with ano-rectal carcinoma may be helped by:
(a) Radiotherapy
(b) Rectal steroids (prednisolone

suppositories bd, betamethasone foam bd, or a prednisolone retention enema daily)

(c) The provision of appropriate INCONTINENCE AIDS

(d) Metronidazole rectally if there is an offensive discharge.

3.10 RECTAL IRRITATION AND DISCHARGE

Both symptoms upset patients by the discomfort they produce.

Discharge produces the additional embarrassment of odour, incontinence and extra work for carers and attending relatives.

CAUSES

1. Rectal/anal carcinoma.

2. Pelvic tumour infiltrating rectal mucosa.

3. Faecal impaction producing faecal leak.

4. Paraplegia with faecal incontinence.

5. Candida infection.

6. Post radiotherapy sloughing of peri-anal skin and mucosa

MANAGEMENT

(a) Rectal carcinoma should always be considered for palliative radiotherapy.

(b) Constant energetic attention to bowel action. In paraplegia and neurological disorders it is often useful to constipate the

patient and empty the bowel manually twice or thrice weekly. This is sometimes less embarrassing for the patient than constant faecal incontinence.

(c) Prednisolone suppositories or prednisolone retention enema bd.

(d) Radiotherapy slough is rapidly improved by application of ripe papaya.

3.11 INTESTINAL OBSTRUCTION

The management of this relatively common condition (due to GI/pelvis malignancy e.g. advanced cervical cancer, colon cancer) is a difficult problem for the doctor caring for the terminally ill.

However, contrary to popular belief, this condition can be managed

at home if a team is willing to give the family medical support.

GENERAL PRINCIPLES

1. Any treatable cause such as post-operative adhesions or faecal impaction should be excluded.

2. Surgery is indicated when the patient's prognosis is still good and a localized blockage is considered likely.

3. Intravenous fluids and naso-gastric aspiration ('drip and suction') are appropriate only in preparation for surgery, but RARELY IF EVER IN TERMINAL CARE.

4. Steroids can reduce tumour mass and may relieve obstruction e.g. dexamethasone 16mgs daily x 4 days then 6mg daily.

5. Medical management of the individual symptoms is usually the most appropriate option in the terminally ill patient.

TREAT SYMPTOMS:

Treatment options can be summarized:

(a) COLIC

- ❖ Regular buccal morphine orally, by rectum (preference), by sub-cutaneous injection or morphine pump. (not always acceptable in African cultures in the home)
- ❖ Hyoscine butyl bromide (Buscopan) 60-120mgs/24 hrs. rectally, by regular subcutaneous injection, or in pump.

(b) CONTINUING ABDOMINAL PAIN

- ❖ Morphine buccal or oral, by rectum, by sub-cutaneous injection or morphine pump.

(c) CONSTIPATION

Simple constipation must be excluded as

a cause. *There is no place for laxatives in small bowel obstruction as the contents are liquid already.* Faecal softeners should only be given in large bowel obstruction. Pushers only exacerbate colic and perforation. It is wise to do PR every 2-3 days and remove contents and insert a suppository or petroleum jelly to aid expulsion.

(d) DIARRHOEA

- ❖ loperamide 4mg prn
- ❖ steroids (dexamethasone 4mg bd)

(e) VOMITING: Most patients will have to vomit but are able to cope with this when the mechanism is explained and the nausea controlled by the measures below.

- haloperidol (0.5 - 1mg bd orally or by sc injection)
- chlorpromazine 10 - 25mg tid (beware of hypotension)
- steroids (dexamethasone 4mg bd)
- metoclopramide 10mgs bd is helpful as long as there is not complete obstruction, because it is propulsive and assists gastric emptying.

(f) DRY MOUTH

- scrupulous oral hygiene, ice to suck, frequent sips of favourite fluids, e.g. sodas, passion juice. Chewing of fruits

to stimulate saliva e.g. pineapple, passion fruit, orange or lemon. These can be spat out after chewing if preferred.

(g) DIET

- The patient should be encouraged to take 'a little of what he fancies.
- Again the taste of food can give a feeling of well-being even if it has to be spat out.

The patient who is dehydrated complains more of a dry mouth than thirst and will be made more comfortable by scrupulous attention to this than by the correction of dehydration

4. URINARY SYMPTOMS

So interrelated are they, it is appropriate to consider here - Incontinence, retention, frequency, strangury and catheter problems.

Causes and management will be considered together.

4.1 INCONTINENCE

MANAGEMENT OF CAUSES:

1. *Urinary Tract Infection* (UTI) is worth treating with an appropriate antibiotic if it can be taken orally but intravenous antibiotics are rarely justified in a terminally ill patient. Antibiotics are not justified if the patient has an in-dwelling catheter. It must be remembered that;

- There may be incidental bacteruria in an old or debilitated person.
- When an indwelling catheter is left for more than a month there is inevitably bacteruria due to changes in the bladder wall. This should not be treated unless there are systemic symptoms.

2. *Structural changes in the bladder* may occur due to tumour and post-irradiation fibrosis for which even catheterisation may not be wholly successful.

3. *Retention with overflow* may be due to

(a) Spinal cord compression. After the patient has been catheterised and steroids commenced, the possibility of irradiation should be considered promptly;

(b) Morphine initiation in the elderly or debilitated. This is usually relieved by an in/out catheterisation followed by bladder drill and is not an indication to stop morphine. It is useful for the Home Care Team to carry a 12G Nelethon catheter in the bag for such an emergency, otherwise the unfortunate patient may be admitted to hospital.

(c) Excessive sedation with hypnotics, tranquillizers, opioids etc.

6. *Vesico-vaginal fistula* (VVF)

This is probably the commonest cause of incontinence seen in Uganda with cases of cancer. It is found in cancer of the cervix and may occur relatively early in the disease. These women are unable to function normally because of the fear of leaking and smell. We have designed a plastic pant, elasticized at the thighs and tied with tape at the waist at each side. This allows the woman to continue with her work using cotton or towelling inside the pants. Give the pattern to a relative or volunteer and they can make it out of plastic.

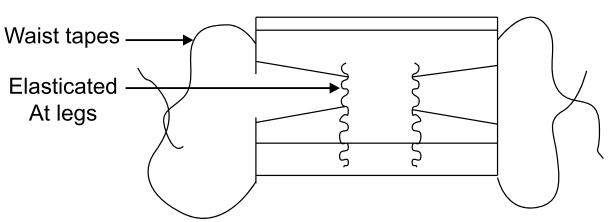


Figure 11: The pattern for plastic support pants for VVF patients

4.2 URINARY RETENTION

1. Drug-induced, particularly by anti-cholinergic drugs, tricyclic antidepressants, opioids (temporary and initial only, see above).

2. Neurological causes, particularly spinal cord compression.

3. Faecal impaction of the rectum.

4. Prostatic carcinoma obstruction bladder neck. Probably all will require a catheter initially, whatever the cause.

In"1" it may be possible to withdraw the drug, keeping in mind the temporary effect of morphine described above, and in "3" evacuate the rectum in the usual way.

4.3 DYSURIA AND STRANGURY

Caused by:

1. Urinary tract infection - see above.

2. Bladder or prostatic carcinoma, particularly affecting the bladder neck.

3. Calculi or retained blood clot.

4. Infiltration into the bladder of a tumour from adjacent organs (rectum, cervix, vagina).

MANAGEMENT:

In all except '1', catheterisation will probably be necessary in order to perform bladder

washouts and deal with incontinence or partial retention often associated with it.

Generalized bladder pain from a bladder carcinoma, may be helped by prostaglandin inhibitors (ibuprofen 400mgs qid) but strong analgesics such as the opioids are almost always needed too and should not be withheld.

Strangury is rare but can be a distressing pain. Try any anticholinergic if available. e.g. propantheline 15mg qid, imiprimine 10-20mgs mane or amitryptiline 25mgs nocte. Failure is common and resort may have to be made to permanent catheterisation.

4.4 URINARY CATHETERISATION

Many ill patients, contrary to expectations, would rather have an indwelling catheter than dribbling incontinence or recurring retention.

The pros and cons of catheterisation need to be explained to the patient and family.

USEFUL HINTS FOR CATHETER CARE

1. Use "Foley" catheters.
2. Do not keep inflating/deflating the bulb or re- inserting different sizes of catheter if the patient develops by-passing.
3. Preferably use catheters with bulbs of 5ml capacity.
4. The simplest bladder washouts are the best in most cases: chlorhexidene 0.05% daily*5days for infection and weekly for

maintenance; saline for debris, deposit and clot removal. Boiled, cooled water can be used to wash out debris in the home. *Carers can be trained to do bladder washouts.*

5. The discomfort of catheterisation in the anxious patient may be avoided by prior administration of oral or rectal diazepam 2 - 5mgs, or morphine 5mg (all given 30 minutes prior to the procedure) or by using an anaesthetic gel introduced into the urethra prior to catheterisation.

6. Haematuria: occurs towards the end of life in about 10% of patients. A bladder washout using silver nitrate 1 in 10,000 can reduce bleeding in severe cases. Reassurance and explanation to the family is required.

5. NEURO PSYCHOLOGICAL

In many African countries, confusion, depression or other manifestations of psychological disturbance may mark a family as having psychiatric disease which can be passed on. This disrupts marriages as well as other cultural plans.

> Every effort should be made to reassure the patient and his family that his behaviour is not, as may be imagined, a manifestation of a neurotic or psychotic state, nor a difficult personality manifesting itself, but due to a disease process.

5.1 INSOMNIA

In our experience this is rare in Uganda once pain and symptoms are relieved together with emotional support.

CAUSES

The aetiology is ill understood but is usually found to be associated with one or more of the following, and each merits attention:

1. Poorly relieved physical distress, which may not be reported i.e. pain and symptoms. Many of our patients have not slept for weeks or months before referral. This is redressed within 24 hours of pain and symptom control.

2. Anxiety, often so mild that it is not apparent during the day. It is vital to ask why the patient thinks he/she is not sleeping, whether they may be worried or have concerns which become more prominent at night.
3. Depression, disturbed sleep pattern may remain the only feature for a long time and failure to explore this and consider a therapeutic trial of an anti- depressant is a common mistake.

All that can be done here is list important points on the commonest used drugs, none of which is ever a substitute for companionship and a carefully tailored atmosphere of safety.

4. Nocturia, which may respond to an anticholinergic at night e.g. amitryptiline 12.5-25mgs.
5. Night sweats, particularly in patients with hepatic metastases, frequently respond to cimetidine 200-400mg, ranitidine 150mg or thioridazine 10mgs each night.
6. Rarely previous dependence on barbiturates, benzodiazepines or alcohol, which have recently been discontinued.

MANAGEMENT

When all have been explored one may still be left with no obvious cause. In this case it is wisest to assume that anxiety and/ or depression are responsible and every effort should be made to explore this and

if not resolved with counselling, prescribe a sedative anti-depressant with anxiolytic properties (e.g.. amitryptiline 12.5-25mg).

The withdrawn patient may do better with imiprimine (25-50mg) at night. Long-acting benzodiazepines, whilst often aiding sleep, usually leave the patient with daytime sedation, (diazepam has a ½ life of 36 hours) poor concentration and/or depression which may be unacceptable. Short-acting benzodiazepines such as triazolam 62.5 microgms (mcgs) (0.0625 mgs) maybe helpful to break a sleepless cycle and is usually only required once or twice. An alcoholic drink at night may help if acceptable to the culture and religion. A candle or spirit lamp left on in the dark room may reassure a patient.

There will remain patients, particularly among confused and older persons in hospital, who have a reversed sleep pattern, awake at night and asleep by day. The routine of nursing attention may need to be adjusted accordingly.

It is worth trying thioridazine 25 mgs or haloperidol 5mgs, at night for a few nights to break the pattern.

5.2 ANXIETY

It is impossible to imagine any very ill or dying patient who will not show some features of anxiety, particularly if he has poorly controlled pain or symptoms or unresolved issues in life.

Even patients with no personality disorder

and no past history of anxiety neurosis will be anxious to a "pathological degree" if:

1. Pain or any other distress is not taken seriously by health professionals and given energetic treatment.

2. The significance to the patient of each new distress is not explored and explained in simple, honest terms, remembering that the significance to the patient may be quite different from that to the professional. Their palpitations may be thought of as "the cancer reaching the heart", sweating as a sign of tuberculosis, while oedema is "renal failure", poor visual acuity as incipient blindness etc.

3. Different health professionals, relatives, friends and carers, give different and apparently conflicting explanations, prognosis and advice.

4. This is particularly common coming towards the end. *Respect for these elders often forces carers to take their advice.*

5. The patient has unrealistic goals, which need discussion and modification.

6. There may be spiritual pain, which needs exploring.

MANAGEMENT

(a) No anxiolytic is as effective as time spent sharing a patient's problem and ensuring he/she is as fully in the picture about the

illness and its features as intelligence, education and state of health will permit. This requires not so much QUANTITY of time spent with the patient as QUALITY of time. The dying are usually acutely aware of how little time is left to them and how busy are their professional attendants, and ask only that these attendants take them and their troubles seriously. When something is troubling them, a few minutes of serious concentrated attention are more valuable to them than half an hour of light superficial conversation.

(b) The best "anxiolytics" are those, which relieve the distressing symptoms, whether appropriate analgesics for pain, steroids for anorexia, laxatives for constipation or anti-emetics for vomiting.

(c) When all else has been tried, only then should the true anxiolytics be prescribed, late at night when anxiety and pain are usually most evident and alarming, when a short half-life benzodiazepine is used.

(d) When tablets cannot be swallowed it is worth remembering that diazepam can be given rectally, (see above).

(e) Panic attacks are best treated by the presence of a reassuring attendant. Diazepam is painful and protein bound in muscle prolonging the half-life. If available, midazolam 5 mg can be given subcutaneously or im and has a very short half life, but this maybe prolonged

in a declining metabolic state as found in the elderly or terminal patient.

(f) When pain is a feature of the condition, and of sufficient degree to merit consideration of an opioid, it should be remembered that morphine remains both the best analgesic and anxiolytic.

5.3 DEPRESSION

Depression is a common and under treated symptom among people living with HIV/AIDS and advanced cancer. It has an enormous impact on quality of life, diminishing people's capacity for pleasure and meaning in life. Patients should therefore regularly be asked about mood and sense of well-being. It is different to "ordinary" sadness, which is appropriate given the circumstances of many patients.

Many terminally ill patients will be profoundly depressed but not suffering from a 'depressive state' requiring an anti-depressant. The injudicious use of an anti-depressant may cause unnecessary sedation, worsening of constipation, an unacceptable dry mouth, halitosis and possibly urinary retention on top of all their other problems.

Doctors and nurses must train themselves to differentiate between "depression" and "misery" or "sadness". There is substantial evidence that most depression is of a reactive type, resulting from inadequately controlled pain and other symptoms.

Pathological depression occurs more in those who spend a long time before dying of a terminal illness. Thus it may be more common in the HIV/AIDS patient on ARVs and should be identified as soon as possible.

DIAGNOSIS:

Depression is nowadays diagnosed according to DSM IV criteria: (See box)

Persistent low mood and at least 4 of following symptoms present for most of day for preceding 2 weeks:

1. Diminished interest or pleasure in all or almost all activities
2. Psychomotor retardation or agitation
3. Feelings of worthlessness or excessive and inappropriate guilt
4. Diminished ability to concentrate or think
5. Recurrent thoughts of death and suicide
6. Fatigue and loss of energy
7. Significant weight loss or gain
8. Insomnia or hypersomnia

Obviously some of these are also common features of any far-advanced disease, particularly cancer and AIDS. The depressive state may present as agitation in the young as well as the old.

MANAGEMENT

Comprehensive medical evaluation is required to optimise symptom control especially poorly controlled pain, which is known to influence depressive feelings. There are other contributors, e.g. steroids, diazepam, efavirenz, CNS disease.

Correctible factors should be treated e.g. switching efavirenz to a different drug.

Even when features of anxiety are also present it is useful rather to prescribe an anti-depressant with anxiolytic properties as the drug of the first choice rather than a simple anxiolytic. Nevertheless, the diagnosis is not an easy one to make and there is often value in giving an anti-depressant as a THERAPEUTIC TRIAL if the patient is expected to live long enough to benefit from it. Remember that 14 days is required to make a biochemical response in the normal patient.

Although there is little to choose between the anti- depressants, certain features are worthy of note:

- *Amitryptiline* is for agitated depression. It is a useful sedative

  when taken at night only.

- *Imiprimine* is for withdrawn depression. Primarily this antidepressant is mildly stimulant - therefore never given after 4pm.

Alternatives to amitryptiline but often not available in Uganda:

1. Protryptiline: Stimulant anti-depressant with no anxiolytic properties
2. Clomiprimine: Anti-depressant but useful when obsessional, ruminative neurotic features are also present.
3. Fluoxetine: (Prozac), now becoming available in some African countries, inhibits the uptake of 5HT. It has less cardiotoxicity and muscarinic effects than amitryptiline. It is less sedative.

There are no indications for mono-amine oxidase inhibitors (MAOIs).

Antidepressants can modify the perception of pain and enable patients to require fewer analgesics.

It cannot be emphasized enough that the principal form of care must be sympathetic support of the patient with an obvious willingness to encourage him to share his every emotion and express every fear.

He will usually benefit from a leisurely chat with a professional more ready to sit and listen than write out a prescription.

Support for the patient and family from the team and other supporters from their religion or from the community can all be of benefit in addressing the emotional and spiritual issues that overlap and influence clinical depression.

5.4 CONFUSION

Confusion is a common and distressing problem. Remember that the patient who is very deaf or very anxious might not be confused at all in spite of what other colleagues might say.

Delirium (previously called "acute confusional state") involves acute alteration in level of alertness, cognition (confusion) and perception e.g. delusional beliefs and hallucinations. It is extremely common in patients with advanced disease and under diagnosed. It tends to occur more acutely, whereas dementia tends to proceed slowly over time and is not usually associated with drowsiness.

CAUSES (not an exhaustive list)

1. HIV invasion of brain cells: often a terminal event in patients not receiving Anti Retro-Viral therapy. In patients receiving ARV's, the confusional state may be more prolonged. It is a condition greatly dreaded by patients in the developed world.
2. Uncontrolled pain, unrecognized discomfort due to urinary retention or severe constipation.
3. Changes in environment, leaving home, transfer from one ward to another.
4. Metabolic disturbance, septicaemia, uraemia, hyper-calcaemia, hypo-natraemia, hypoxia, severe anemia.

5. Cerebral metastases.
6. Cryptococcal meningitis or other opportunistic meningitis in the immuno-suppressed. This is a temporary condition if the infection is controlled.
7. Cerebrovascular disease.
8. Drug induced, for example psychotropic drugs, barbiturates, benzodiazepines, cimetidine and hypertensive therapy in the elderly. Other medications include AZT, efavirenz, steroids, amphotericin, high-dose sulfamethoxazole/trimethoprim, and opioids (rare but accompanied by other features of opioid toxicity e.g. myoclonus, drowsiness, nightmares or vivid dreams), tricyclic anti-depressants.
9. Drug withdrawal may also precipitate confusion, for example, alcohol, benzodiazepines, barbiturates, opioids.
10. Infections even when not HIV related
11. Constipation
12. Terminal delirium: this is a common finding towards end of life; 3 subtypes: Hypoactive (commonest, more difficult to recognize), hyperactive (with agitation, combativeness, etc) and mixed. May occur in setting of active and imminent death.

MANAGEMENT

1. Always treat as a sane adult. Reality orientation by family, reminding of the

place, time and day etc. Explain any interventions and procedures.

2. Alleviate any identifiable cause if possible and if appropriate.

3. Confident handlings by a limited number of staff and with a relative always close at hand.

4. Sedation (if indicated for the patient's, relatives' and staff's sake). Small studies of hospitalized HIV patients have demonstrated that standard doses of typical antipsychotics (eg, haloperidol 0.5mg BD in elderly- 1.5-5mg BD in younger patients), are more effective and safe than benzodiazepines. Thioridazine 25-50mg up to 6 hourly (but once at night is often enough) orally, is particularly effective in elderly with paranoia component. Newer atypical antipsychotics e.g. risperidone, olanzapine cause less extrapyramidal and sedation side effects than the typical antipsychotics but are still expensive.

Treatment involves trying to establish and address underlying causes, while concurrently treating with anti-psychotic medications in low dose- to reduce agitation and altered perceptions.

6. SKIN AND RELATED DISORDERS

Caring for the skin and mucous membranes of patients with cancer and/or AIDS who are near the end of their lives can be challenging. Skin disorders can be very troubling to patients and cause a lot of discomfort. Lack of activity as well as excessive loss of weight as end of life approaches can lead to the development of skin breakdown.

Recognition of potential causes of skin and mucous membrane disorders is very important because dying patients do not have the luxury of waiting for diagnostic test results before therapy is started. Treatment planning is based on clinical identification of the most likely diagnosis, and therapy is instituted as soon as possible to effect palliation of discomfort.

6.1 PRURITUS

CAUSES

1) HIV/AIDS

2) Pre-existing skin disease (eczema, psoriasis, infestation).

3) Dry skin (particularly senile pruritis).

4) Obstructive jaundice.

5) Melanomatosis.

6) Hodgkin's disease.

7) Anxiety state.

8) Allergic reaction.

9) Paraneoplasic syndromes.

Near the end of life the causes may be related to the patient's primary illness, co morbid conditions, allergies or infections.

Management:

(1) HIV/AIDS: Drug eruptions are particularly common in patients who are HIV positive, presumably as a result of immune dysregulation (initially and responds to 1% hydrocortisone cream), altered drug metabolism, and polypharmacy. Later pruritis is due to multiple opportunistic skin infections and often responds to rinsing the skin after bathing with 0.05% chlorhexidene solution. This gives results within 10 days. HAART has been shown to reduce/ alleviate common pruritic eruptions in AIDS.

(2) In obstructive jaundice, if biliary stenting is unavailable, it is worth trying:

- Haloperidol 0.5mg bd or 2mg at night. (*not sure if any evidence for this)*
- Steroids (dexamethasone 2mg bd, reducing to 1mg/day)
- Prednisolone 15mgs reducing to 10 mgs daily
- Ranitidine 150 mgs od
- Rifampicin 150 mgs bd – acts as an enzyme inducer. Do not use if on ARVs.
- Antihistamine eg chlorpheniramine 4 mgs tds.

(3) AS GENERAL NON-SPECIFIC MEASURES - in addition to treating any pre-existing condition:

- Emulsifying ointments.
- Sodium bicarbonate washes as often as desired by the patient (one tablespoon of powder in the smallest volume of water sufficient to dissolve it). Patients often report this as more effective than any other measure.
- chlorpheniramine maleate 4mg tid. 1% menthol aqueous cream or lotion.
- Weak topical steroids (1% hydrocortisone).
- Cold fan playing on the exposed skin.
- Occasionally a short course of oral steroids in combination with an anti fungal agent is worth a try in KS or AIDS.

- Patients need to be advised to keep their nails short and to rub itching skin gently to prevent skin damage[13].
- It should be known that there is no 'broad spectrum' anti-pruritic drug. Low sedative H_1-antihistamines relieve itch only when it is histamine-mediated.
- Skilled nursing more usually helps pruritus than any medical measures.

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13 R Twyross et al. Q J Med 2003; **96**: 7-26

6.2 HYPERHIDROSIS (EXCESSIVE SWEATING)

This distresses patients because of the inevitable discomfort and embarrassment. They are frightened in case they have another disease infectious to their relatives, in addition to cancer.

Tuberculosis and AIDS are associated in Uganda and the fear of both diseases is very real.

CAUSES

1. Intercurrent infection, including TB. (except in the final days of a terminal illness it is worthwhile treating an intercurrent infection if, by doing so, the patient's comfort is ensured and condition is reversible
2. Toxaemia associated most commonly with liver metastases.
3. Lymphomas.
4. Morphine in high doses.

MANAGEMENT

1. Try to investigate and treat the cause.
2. If fever is present try paracetamol, which may increase the sweating but bring down the temperature and thus reduce sweating for a time.
3. Cimetidine 200-400mg each night, can be

of help.

4. Indomethacin 25mgs or ibuprofen 200mg qid after meals orally, propranolol 40mg tid (if not contra-indicated by bronchospasm or cardiac failure).

5. Steroids (dexamethasone 2-4mg/day). 67

6. Thioridazine 10mgs at night can be effective.

7. Skilled nursing, frequent sponging and appropriate advice about clothing and bedding, assist most patients more than any medical measures.

6.3 OEDEMA AND SWELLLING

Kaposi's sarcoma is probably the commonest reason for swelling of legs and other parts of the body particularly the face, presenting at Hospice Uganda. The woody hard infiltration of the skin by the tumour gives areas of distension with blockage of small vessels and lymphatics, giving occasionally an element of fluid retention as well as thickening of the skin. This is compounded by opportunistic infections in the skin. Consideration needs to be given to ARV treatment, which in some instances may improve condition. If available and affordable chemotherapy can give palliative benefit, however it is an unaffordable option for many.

If infections are controlled then a trial of steroids e.g. 8 mgs of dexamethasone for one week, is worth a try. If successful, withdraw slowly. Pain can be extreme, especially when the soles of the feet are involved. Pain relief is the first priority. Then treat each identified factor contributing to the discomfort.

UNILATERAL UPPER LIMB

LYMPHOEDEMA:

Massage of the arm, starting with the hand and working towards the axilla is helpful. During the day the patient should wear a firm elastic bandage if tolerated. Elevation of the arm on pillows or in a sling suspended from a drip stand or head of the bed may be effective but is usually impractical because shoulder movements are painful and limited.

Good skin care is essential, keeping the skin moist with aqueous or other moisturising cream. Dry skin will break down with subsequent infection.

Dexamethasone 6mg bd x 3 days reducing to 2mgs relieves pressure. Morphine (sometimes in high doses) may be required for pain and works if titrated accurately

BILATERAL UPPER LIMB

Superior vena cava obstruction, with venous distension in the area drained by the superior vena cava, infra- orbital oedema and upper limb cyanosis. Its management with prompt radiotherapy, chemotherapy, or high-dose

dexamethasone is dealt with in Section 2.4

UNILATERAL LOWER LIMB

The three principal causes in terminal care are:

1. Venous and/or lymphatic caused by a pelvic tumour. Radiotherapy and chemotherapy should be considered if available.

2. Deep venous obstruction: The decision whether or not to give anticoagulants is a difficult one requiring a careful assessment of the whole clinical picture, the tempo of the disease and the likely prognosis. Anti- coagulants are rarely indicated in terminal disease because of the tendency to haemorrhage.

3. Infection, whether cellulitis, lymphangitis or deep tissue infection from nearby tumour, treated usually with appropriate antibiotics, bed rest and analgesics as required.

BILATERAL LOWER LIMB

The three principal causes in terminal care are:

1. Lymphatic and venous obstruction by a pelvic tumour, managed by radiotherapy, high-dose dexamethasone (with less success than in superior vena cava obstruction) and diuretics, preferably spironolactone 75-400mgs daily together

with frusemide 40- 200mgs daily, monitoring for signs of dehydration, low blood pressure and renal failure developing.

2. Cardiac failure, treated in the routine way.

3. Hypoalbuminaemia, either from dietary deficiency or loss in ascitic fluids. Rarely is it appropriate or possible to correct this in a terminally ill patient.

Frequently lower limb oedema troubles the patient by appearance more than discomfort and is sometimes the result of sitting for prolonged periods with the feet dependent. This is not an indication for diuretics, with the resultant need for careful monitoring of electrolytes, but for elevation of the feet, leg movement in walking or passive movements, support stockings, and reassurance that this is not cardiac or renal failure. Support stockings are not usually practical in a hot country like Uganda. It must be remembered that oedema is usually multifactorial in aetiology and treatment of any contributing factor is worthwhile.

6.4 FUNGATING TUMOURS AND ODOURS

Even when skilled nursing is provided for the patient with a fungating tumour, he will be distressed by any odour because of the embarrassment and its ability to isolate even further from relatives and friends. Denying the existence of a bad smell will never comfort

a patient acutely aware of it! In time, some patients, but not their relatives, may become less aware of the smell.

MANAGEMENT

a) Regular cleaning of the fungating tumour with saline. This can be made up mixing rock salt and boiled cool water in the home.

b) Radiotherapy may be an option.

c) Metronidazole[14] tablets crushed and placed on the fungating area, removes the smell and dries up the discharge. It also provides haemostasis and clears the infection caused by the anaerobic organism. Metronidazole pessaries or tablets can be inserted into a sinus or orifice leading to a smelly growth. Insert once daily. These are useful in rectal and cervical cancers.

14 Metronidazole is not so effective by mouth because it cannot reach the organism as there is no blood supply into an area of dead tissue

7. EMERGENCIES IN PALLIATIVE CARE

For each emergency we must ask ourselves these questions:

- What effect will reversal of the symptom have on patient's overall condition?
- What is your medical judgment?
- What does the patient want?
- What do the carers want?
- Could active treatment maintain or improve this patient's quality of life?

7.1 PAIN EMERGENCIES

Severe uncontrolled pain

- Severe uncontrolled pain (on initial presentation or a sudden escalation of pain) is an emergency; the patient needs constant attention until the pain is controlled.

- The immediate goal is to reduce the pain and allow the patient to rest. The patient will settle enough to facilitate assessment.

Treatment:

- Give a dose of oral morphine 5-10mg, or, if already on morphine, give a break through/rescue dose (equivalent of the 4 hourly dose) immediately.

- Response to oral morphine normally begins in 30minutes.

- Response is most rapid with IV injection but needs to be given slowly. (s.c., im. or IV slow injection). However in HAU it is usually oral morphine that is used successfully.
- If already on oral and changing to parenteral, give the correct dose by dividing the patient's regular oral dose by 2. *E.g. if patient was on 15 mg morphine orally every 4 hours, an appropriate SC/IM stat dose would be 7.5 mg.*
- Reassess response to dose; if SC injection is given, after 20 minutes if IV injection is given after 5 minutes, if oral dose is administered, after 40 minutes.
- Repeat dose if pain is still unrelieved after this time.
- Do not leave until you are sure the patient is more comfortable.
- Titrate the dose of regular morphine based on stat doses required for comfort E.g. if a patient was on 10 mg of morphine every 4 hours, but required a rescue/breakthrough dose of 15mg to be effective, the regular dose of morphine needs to be increased to at least 15mg every 4 hours with advice that a rescue/breakthrough dose can be taken PRN
- Assess the regular dose again in a few days, according to directions for break through doses adjustment (P.)

- When the patient is comfortable, complete thorough pain assessment.
- Consider specific causes of severe sudden and exacerbation of pain.

Vertebral collapse

- Usually occurs in a patient with known bony metastases.
- Manage pain as above for Pain Emergency (7.1.1). It is sometimes necessary to double or triple the usual dose of morphine for several weeks, reducing again by titrating against pain.
- Always review a patient's neurology and ensure that there are no clinical signs of spinal cord compression.
- Escalating back in radicular distribution in a patient with spinal mets, is classic for spinal cord compression.
- Palliative radiotherapy helps with bone pain, but takes weeks to have maximal effect.

Pathological Fracture

- Classically, this pain is very severe, acute in onset and worse on the slightest movement. There may be associated limb deformity.
- Immobilising the fracture through orthopaedic surgery is the ideal way of dealing with the situation. Splinting and comfortable positioning are very important in achieving pain control,

when surgery isn't possible.

- If the limb is not immobilized, any movement will continue to provoke severe pain which is difficult to control with medication alone.
- Patients with metastatic breast or prostate cancer, may survive months or years after sustaining a pathological fracture, and thus should definitely be considered for surgery.
- Patients with other cancers such as melanoma or bronchogenic carcinoma may only live for a short time and the decision may be more difficult.
- Ensure that adequate analgesia is provided in the same way as for pain emergencies (7.1.1).
- For predictable movements e.g. if a patient knows he/she will be getting out of bed in the morning, give a dose of morphine 45 mins in advance before movements to try to lessen pain during movement.

  Demonstrate practical methods to relatives of how to move patients with fractures.

Biliary /Ureteric Spasm:

- The best treatment for biliary or ureteric spasm is an oral, im or IV NSAID like Diclofenac 75mg.
- If this fails to relieve pain in 20 minutes, should be supplemented with an opiate:

morphine 5-10mg oral or sc/im/iv.

- For the patient who is already receiving opiates, give double dose of morphine orally or the equivalent sc/im/iv.

Bladder Spasm:

- Transient but often excruciating sensations felt in the suprapubic region and urethra.
- Spasms may relate to local cancer, treatment like radiotherapy, infective cystitis or mechanical factors like a catheter.
- The cause should be treated if possible, explanation given and analgesics to relieve background pain.
- Drugs that reduce Detrusor (bladder muscle) sensitivity like anticholinergics (Amitriptyline 25 – 50mg at night, propantheline bromide 15 mg bd); Buscopan (hyoscine butylbromide 10mg); NSAIDS (naproxen 250 – 500mg bd) can also be helpful.
- Secondary muscle spasm may be helped with oral diazepam 5mg stat and 5 – 10mg at night. If nerve compression pain is also a problem, dexamethasone 4 – 8 mg daily can be a helpful addition.
- Review and follow-up closely to ensure adequate comfort and if possible provide with a telephone number so that he/she can contact the service for advice if needed.

7.2 MEDICAL EMERGENCIES (SEE ALSO SECTION 2)

Acute Dyspnoea/Breathlessness:

- Dyspnoea can be a very frightening sensation, therefore relieving this symptom and providing reassurance are vital for comforting the patient.
- Simple measures are often helpful;
  - a patient should not be left alone, and a calming environment gives much relief
  - increase air movement over the patients face (fan/window)
  - explain what is happening
  - sit the patient up if possible
  - assess patient looking for cause.
- Treat reversible causes where possible and if appropriate, the health professional can manage the condition by administering antibiotics for infection, pleural tap for large effusion, steroids for bronchial or tracheal obstruction or PCP.
- Consider disease-modifying treatments such as radiotherapy and corticosteroids.
- Low dose morphine 2.5 – 5mg 4 hourly is useful in relief of dyspnoea.
- If already on morphine for pain relief, increase the 4 hourly dose by increments of 2.5mg until dyspnoea is controlled.

- Diazepam 2.5- 10 mg BD (or alternative benzodiazepine) is effective both as an anxiolytic and in reducing the sensation of breathlessness.
- It has a long duration of action and may accumulate in the elderly; in whom low doses at longer intervals is usually suffice.

Spinal Cord Compression (SCC):

- SCC occurs in 3% of patients with advanced cancer, most commonly occurring in cancers of the breast, bronchus and prostate but also associated with renal cell carcinoma, lymphoma, multiple myeloma, melanoma, sarcoma, head and neck cancer.
- In 20% of cases, compression of the cord occurs at more than one level. The commonest site for compression is in the thoracic spine (70%), followed by the lumbar spine (20%), and cervical spine (10%). Below the level of L2 compression is the cauda equina not the spinal cord.

Compression of the spinal cord is usually caused by metastatic spread to the vertebral body or pedicle (85%). Tumour extension through the intervertebral foramina (lymphoma) or more rarely due to a primary vertebral bone tumour or haematogenous spread into the epidural space.

Presentation:

- Spinal cord compression usually presents with back pain (<90%). Typically, pain is the earliest sign. It may be;

  - a bony pain due to vertebral metastases

  - radicular or nerve root compression

  - a diffuse band like pain

  - unpleasant sensation below the level of compression.

Escalating back pain (i.e. increasing in severity rapidly) that is difficult to relieve should always raise high suspicion of spinal cord compression-

DO NOT wait for the patient to become immobile before treating for SCC.

- Pains are often exacerbated by straining, coughing or sneezing. Sensations of sharp shooting pains electric shock like sensations down the legs may also indicate spinal cord compression.

- Pain can usually be elicited by percussion of the vertebra within one or two vertebrae of the compression, but absence of tenderness in presence of suggestive history does not rule out the diagnosis.

- Following escalating back pain, weakness of limbs tends to occur in continuing SCC. Patients often initially describe their legs as 'heavy' or 'uncoordinated'. A history of escalating back pain and heavy legs is sufficient to consider treating for SCC.

- Later signs include loss of sensation, paralysis and loss of sphincter control.

- Patients may be unaware of sensory changes i.e. anaesthesia or paraesthesia until they are carefully examined, yet this is relatively common in advanced SCC. Sphincter dysfunction causing urine retention and constipation tend to be late signs.

Investigation:

- Plain X-rays show vertebral metastases or collapse at the appropriate level in 80% of cases.

- Normal x-ray does not outrule diagnosis. (Magnetic Resonance Imaging (MRI) is the investigation of choice when available. CT scan or myelograms can also be useful. Access to such tools is not usually possible in developing countries.)

- The single most important prognostic indicator with Spinal Cord Compression is neurological status before initiation of treatment. i.e. The less damage the better the potential for recovery.

Patients with paraparesis do better than those with total paraplegia. Loss of sphincter function is a bad prognostic sign. Recovery is more likely after lesions of the cauda equina.

Treatment:

Steroids

- Corticosteroids reduce peri-tumour oedema and inflammation and often lead to early improvement and pain relief. Dexamethasone is usually given in high dosage: 16mg - 24 mg daily in divided doses with the first dose given IV if possible.

Radiotherapy (RT)

- Referral for urgent radiotherapy should be made, if available and appropriate (e.g. if a patient has an advanced disease and lives 60km from RT centre, requiring driving over bumpy roads, this may no longer be appropriate).
- It is usually given to a field that includes one or two vertebrae above, and below the compression.
- This treatment is usually given concurrently with steroids, and acts to prevent further tumour growth and compression of the cord
- If there is a good response to concurrent radiotherapy, dexamethasone can be tapered down every 3 days to the smallest maintenance dose possible

i.e. lowest dose at which there is no neurological deterioration/deterioration in pain control.

- Sometimes after radiotherapy, it is possible to stop the steroids completely without worsening/recurrence of SCC.
- Patients unable to access radiotherapy treatment often gain some neurological improvement following a course of dexamethasone. Administer a high dose initially and taper down every 3 days to smallest maintenance dose possible. i.e. lowest dose at which there is no neurological deterioration/deterioration in pain control. If there is subsequent worsening, the dose can be increased.
- Over time, it is likely that complete SCC will occur despite steroids, in this case, they should again be reduced and ultimately stopped, provided pain is controlled.
- Titrate analgesia and if already on morphine, dose is likely to need substantial increase in the early stages of SCC. (See Section on Pain.) This should happen at the same time as using steroids and RT.

MANAGEMENT OF PARAPLEGIA:

- Particular attention should be paid to continence, bowel care and pressure areas. Patients with urine retention will require catheterization. Catheter care daily is required including bladder

washout with boiled cooed water daily, to avoid debris accumulation and blockage of catheter. Weekly wash out with and with 0.05% chlorhexidene weekly. If infection occurs, avoid systemic antibiotics and give chlorhexidine 0.05% washout daily for a week.

- Those with complete cord compression unresponsive to treatment and constipation are likely to require enemas or manual evacuation of rectum regularly, with a regular routine arranged for convenience, privacy and less smells.
- Helping the patient to sit out for periods and regular changing of position, will be required to prevent pressure areas. Massage of pressure oints by a carer three times a day can also assist using wet soap but not methylated spirits as in the past.
- Family members can be taught how to care for their relative in this way.
- Advising both the patient and family about SCC and its effects, including realistic assessment of prospect of recovery, is very important. In practice, recovery will usually occur early if it is going to do so i.e. improvement in condition occurring within days/weeks.
- After weeks of immobility, recovery is increasingly unlikely, and a difficult prospect for anybody to face, it is kinder to be truthful with the patient at this

stage than to suggest future recovery

- Creating such false hope, even when well intended, is unfair to the patient and it often leads to huge efforts, expense (often paying for expensive physiotherapy, urging patient to try harder etc.) and ultimately to huge frustration and disappointment when there is no improvement, despite all their efforts and promises. This may damage the relationship between the you and the patient, if s/he realises that s/he hasn't been told the truth. Even if you have to break bad news, it should be delivered appropriately to the patient.

Haemorrhage

In the developed countries, bleeding of some kind affects about 20% of patients with advanced cancer and in approximately 5% of patients; it contributes significantly to their death. External catastrophic bleeds are less common than hidden internal bleeding.

Bleeding may be due to:-

1. Blood vessel invasion, erosion and subsequent rupture.
2. Ulcerative effects of local infections at vessel sites
3. Underlying bleeding disorders e.g. reduced platelets, reduced clotting factors

- Severe bleeding e.g. massive

haemoptysis or haematemesis is terrifying for the patient, health professionals and the relatives.

The first rule of management is that the patient should not be left alone until the bleeding is controlled.

- If there is a risk of bleeding, anticoagulants such as wafarin should be stopped or kept at the lowest possible doses.
- If GI bleeding, stop NSAID and consider PPI or H2 antagonist. If likely to survive, support with fluids and transfusion as appropriate.
- Consider radiotherapy referral for haemoptysis from lung tumours, KS, bleeding due to bladder ca and rapidly growing erosive tumour.
- If history of smaller bleeds, consider transexamic acid 1g QDS if available. (Antifibrinolytoic agent).
- For surface bleeding from tumour areas, consider gauze soaked in adrenaline (1ml) or transexamic acid applied topically.
- If risk of severe bleeding, (if history of previous one, if large erosive tumour near carotid artery etc) dark towels can be kept nearby for family (as blood looks very frightening for the patient on white/pale surface) and sedation could be kept in house/nearby, if in hospital with instructions on how to use

it. E.g. midazolam 10 mg buccally/SC or diazepam 10 mg PO/PR (in order to lessen anxiety and fear in the event of catastrophic bleed).

Superior Vena Cava Obstruction (SVCO) (also section 2)

The superior vena cava drains venous blood from the head, neck and upper thorax into the right atrium. Obstruction of this vein (SVCO) is usually caused by:-

1. External compression by tumour or lymph nodes
2. Direct invasion of the vessel wall by tumour
3. Thrombosis of ht vessel.

- SVCO are most commonly lung cancers 75% (commonly small cell carcinoma), lymphoma 15% and other cancers including; breast, colon, oesophagus and testis.
- SVCO without treatment can progress into thrombosis, cerebral oedema and death, in a few days.

Presentation:

- Symptoms of SVCO include swelling of the face, neck and arms, dyspnoea, headaches, visual changes, dizziness and fits.
- Signs include; engorged conjunctiva, peri-orbital oedema, dilated neck veins and collateral veins on arms and

chest wall. Late signs include; pleural effusions, pericardial effusion and stridor.

- Diagnosis of SVCO is clinical. (Can be confirmed by a chest X-ray showing a widened mediastinum, or CT scan when available and affordable).

Treatment:

- Advanced SVCO has poor prognosis and may not be reversible.
- Sit patient up in comfortable position,
- Give high dose corticosteroids e.g. dexamethasone 16mg oral/iv, reducing slowly over 10 days or until symptoms reoccur then fix a dose to prevent further symptoms.
- If available, radiotherapy should be considered together with high dose steroids to prevent initial swelling and worsening of symptoms during treatment. Improvement usually occurs within 72 hours.
- At the same time, treat dyspnoea symptomatically with morphine and/or benzodiazepine (as per breathlessness section)

Tumour lysis syndrome

This is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia and is caused by the destruction of a large number of rapidly proliferating

neoplastic cells. Acute renal failure occurs frequently from precipitation of urate and calcium phosphate in the renal tubules.

It is often occurs with the treatment of Burkitt's lymphoma, other high-grade lymphomas, and leukemias within 1-5days of chemotherapy as the malignant cells die. Lactic acidosis and dehydration may contribute to the precipitation of uric acid in the renal tubules.

Patients are at risk of deterioration and death from dehydration, hyperkalemia, acute renal failure and arrhythmias. The likelihood of tumour lysis syndrome is related to the tumor burden and renal function. Management is by pretreatment evaluations (complete blood count, serum chemistry evaluation and renal function tests, urine analysis, ultrasonography).

The standard preventive approach consists of allopurinol, urinary alkalinization, and aggressive hydration. Cautiously administer bicarbonate for acidosis. Rasburicase is given when other measures can not lower urate levels adequately. Dialysis may be necessary.

Seizures

Seizures can be caused by the tumor itself, metastases, metabolic disturbances, radiation injury, cerebral infarctions, or by CNS infections.

Treatment: Abolish active seizure with benzodiazepine (eg diazepam 10-20mg) then give anticonvulsive treatment with

phenytoin 18mg/kg/day. Prophylactic anticonvulsant therapy is not recommended unless the patient is at a high risk for seizures (eg melanoma primary or hemorrhagic metastases). Phenytoin is a hepatic enzyme inducer, therefore adjustment of other drug doses may be required.

Neutropenia and fever

Low white cell counts (less than 1000/microLl) may occur with cytotoxic chemotherapy, and fever occurring with it is a medical emergency. However hypothermia, hypotension, or clinical deterioration as the initial signs of occult infection may occur. Causative organisms are varied but commonly are enteric organisms (eg E coli) and Staphylococcus.

Management includes empirical broad spectrum antibiotics. Cultures should be performed. Treat for 14days or longer guided by clinical response and culture results. Regimens are often multi-drug eg aminoglycoside (avoid gentamicin) with a cephalosporin (eg ceftriaxone or ceftazidime).

Raised intracranial pressure

- Common with cancers that metastasize to the brain (lung, breast cancers and melanoma). Clinical features are: headache, nausea, vomiting, behavioral changes, seizures, and focal, progressive neurologic changes, papilledema with visual disturbances and neck stiffness. Occasionally the onset is abrupt (often from hemorrhage into the metastasis), resembling a

stroke. The tumor mass and surrounding edema may cause obstruction of the circulation of cerebrospinal fluid, with resulting hydrocephalus or herniation syndromes.

- Treatment: Hyperventilation and infusions of mannitol (1–1.5 g/kg) every 6 h. Dexamethasone is the best initial treatment for all symptomatic patients with brain metastases. Radiotherapy if available.

Haemoptysis

Hemoptysis (coughing up >600 mL of blood produced in 24 hrs) is often caused by lung cancer or endobronchial metastases of other cancers or with cavitation of lung with fungal infection esp Aspergillus sp. In such conditions bleeding maybe the terminal event and families can be prepare for this. When respiratory difficulty occurs, hemoptysis should be treated as an emergency. However often it is a terminal event and then conservative treatment of symptoms while keeping calm and assisting the family to be calm, is essential.

Morphine overdose:

- Respiratory depression with morphine can occur but usually due to dosing errors or IV administration.
- Morphine does not usually cause respiratory depression when used orally and titrated gradually against pain. (Pain is an antagonist to the central

effects of opioids.)

- Signs of morphine overdose include: reduced respiratory rate, excessive drowsiness, pinpoint pupils and twitching.
- If there is no life threatening respiratory depression, hydration with IV fluids, close monitoring and subsequent reduction in the morphine dose is often sufficient to treat the patient.
- Morphine overdose, if life threatening can be reversed by Naloxone, an opiods antagonist. If administering Naloxone it is important to titrate it against respiratory rate i.e. give a sufficient dose to ensure that the respiratory rate returns to normal. If the morphine is completely reversed, excruciating pain may ensue for the patient.

7.3 SURGICAL EMERGENCIES*:*

Acute Urinary Retention: (see section 4)

- Urinary retention or severe hesitancy usually requires catheterization for comfort. If the urethra is completely blocked as in advanced cancer of the penis, then suprapubic catheter is necessary.

  Acute retention presents with severe abdominal pain and a palpable bladder on examination.
- Retention may occur due to urine infection, enlarged prostate due

to benign prostatic hypertrophy or prostate cancer, advanced cancer of penis impacted faeces, anti-cholinergic drugs (tricyclic antidepressants, chlorpromazine, and hyoscine), a late feature of spinal cord compression, clot retention, or very rarely due to opioids.

- Urinary retention due to clot retention following bleeding from the urogenital tract requires catheterization and bladder washouts.
- A selective alpha blocker (e.g. indoramin) can be used to relax urethral smooth muscle in prostatism and can improve urine flow. Care is needed as it can cause postural hypotension.

Intestinal Obstruction (see 3.11)

Is due to blockage of the intestinal lumen or a lack of normal propulsion, which prevents or delays intestinal contents from passing along the gastro intestinal tract. It is commonest in ovarian cancer and often heralds terminal stage of the disease. Usually there is more than one block or insipient block due to peritoneal metastases so surgical intervention is contraindicated. The main approach is to keep the patient comfortable by controlling symptoms. (section 3.11)

8. OTHER SYMPTOMS AND INFECTIONS PRESENTING IN AIDS PATIENTS:

8.1 SKIN AND MUSCLE INFECTIONS

These include recurrent boils, itchy skin rash, pyomyositis, fungal infections, eczema, psoriasis, Herpes simplex, Herpes Zoster, mulluscum contagiosum, scabies.

MANAGEMENT:

Abscesses and pyomyositis:

(a) Clean open wounds and ulcers and sprinkle metronidazole powder if smelly.

(b) Drain abscesses.

(c) Use broad spectrum antibiotics if appropriate.

(d) Use the analgesic ladder in acute phase, reducing as recovering. This is especially important in pyomyositis.

Fungal infections:

Whitfield's ointment or other available antifungal cream.

Scabies:

This can be severe in AIDS patients. It should be suspected in atypical irritant skin infections. There maybe crusting and nodules. Benzyl benzoate applied for three days after bath avoiding head and neck. Leave on for 24 hours. Lindane or melathion may be required

if not responding and if available.

Herpes Zoster: (see section 1.6)

8.2 OESOPHAGITIS: (see section 3.5)

8.3 MENINGITIS:

PRESENTATION OF MENINGITIS:

Fever

Headache

Neck stiffness (often absent in cryptococcal meningitis)

Pain

Confusion

Convulsions

localizing signs

CAUSES OF MENINGITIS IN AIDS:

- bacterial (pneumococcal,
- meningococcal)
- TB viral (HIV, others)
- fungal (cryptococcal)
- protozoal (toxoplasmosis)

MANAGEMENT:

1. Treat underlying cause eg. amphotericin/ fluconazole for cryptococcal meningitis.

1. Control of pain and symptoms:
Try to diagnose clinically if there is raised intracranial pressure. Look for photophobia; headache worsens on Valsalva manoeuvre

(straining to pass stool or coughing) maybe projectile vomiting without nausea. Papilloedema noted on ophthalmoscopy if available.

(a) The pain of cryptococcal meningitis is very severe but it responds well to the use of the analgesic ladder. Care to reduce analgesics slowly as recovery takes place.

(b) Control convulsions commencing with phenytoin 100mgs tds.

(c) Manage confusion if occurs. . This may vary on a day-to-day basis. Explain reality orientation to relatives and continue to treat patient as a mature adult. Use haloperidol as described in delirium section, if required.

(d) Support of patients and relatives with explanation of cause of symptoms and reason for management.

8.4. BLINDNESS:

PRESENTS WITH

- impaired vision or progressive blindness.
- May initially be unilateral.
- May have associated headache or confusion.
- On examination: soft exudates or haemorrhages in the retina.

Causes of Blindness in AIDS
CMV retinitis
Optic neuritis
Retinal disorders
Anterior or posterior chamber disorders

MANAGEMENT:

Ganciclovir or foscarnet trisodium by infusion for CMV if available. Control headache. Counselling and practical help for blindness if necessary.

NB: When recommending expensive and often unobtainable treatment, must explain to relatives and patient that lost sight will not be recovered, but treatment *may* prevent further extension of the blindness.

9. OTHER DISTRESSING SYMPTOMS:

9.1 WEAKNESS AND LETHARGY

Fatigue is one of the commonest symptoms reported in adults and children with cancer and HIV/AIDS. While an inevitable feature of end-stage disease, in earlier stages it is frequently multi-factorial. Therefore it is important to consider whether there are underlying reversible components.

MANAGEMENT:

Treat reversible causes;

1. Anaemia: although anaemia is acceptable in the cancer and/or AIDS patient coming towardsthe end of life, anaemia earlier in the disease should be corrected and weakness can be improved. However weakness due to anaemia is usually secondary to a haemorrhage and it is amazing how the body adapts to slow onset anaemia.
2. Excessive sedation or analgesia.
3. A true depressive state, which might benefit from antidepressant (see Section 2.24).
4. HYPERCALCAEMIA, present in 12-15% with advanced cancer according to literature from the more developed countries. (see Section 8.2)
5. HYPOKALAEMIA sometimes worthy of correction.
6. ADRENAL FAILURE either because of hypophysectomy, adrenalectomy, and tumour deposits in the pituitary or adrenals, or failure to take replacement therapy.

MEDICATIONS:

Dexamethasone in low dose has been used as short-term measure for low energy in cancer patients, but in many HIV patients, this will not be appropriate because of its

potential side effects. Dose usually used for this indication is 2-4mg/day. Effect tends to wear off after a few weeks.

Non-Drug Measures: Practical fatigue management advice may help- prioritising activities and saving energy for most important/enjoyable activities, enlisting help with other activities e.g. from extended family, taking short breaks as needed during day etc.

9.2 HYPERCALCAEMIA

CLINICAL FEATURES
Tiredness anorexia
Nausea vomiting
Constipation thirst
Polyuria drowsiness
Confusion coma
Exacerbation of pain

Hypercalcaemia is a complication commonly associated with multiple bone metastases and less commonly can be caused by the ectopic production of parathormone by a tumour. Subclinical hypercalcaemia was shown to occur in 20.9%[15] of breast cancer patients in Uganda's National referral hospital in Mulago, but because its manifestation is non-specific this electrolyte disorder is underdiagnosed in cancer patients.

15 Mwebesa E, Prevalence of Hypercalcemia among breast cancer patients in Mulago Hospital; MMed Dissertation, 2009

- Hypercalcaemia means a serum calcium greater than 2.60mmol/1. 'Corrected Calcium' is used if the serum albumin is low (add 0.02mmol/I to the calcium level for every 1g/I albumin less than 40 g/I).
- It is commonly associated with; squamous cell carcinoma, head and neck cancer, cancer of the breast and cancer of the bronchus. It may also occur in renal cell carcinoma, cervical cancer, oesophageal carcinoma and haematological malignancies such as myeloma. (It is relatively rare in adenocarcinomas)

Symptoms include: thirst, polyuria, constipation, abdominal pain, drowsiness, confusion nausea and or vomiting, unconsciousness and death. Cardiac arrhythmias occur at high levels.

- Intravenous fluids correct dehydration associated with hypercalcaemia, but have little effect on the calcium.
- Bisphosphonates e.g. pamidronate, (not usually available in resource- poor countries because they are expensive) reduce the calcium if given intravenously. Care must be taken to hydrate the patient well prior to administration of Bisphosphonates . The dose may need repeating 3 – 4 weekly.
- Steroids may lower the calcium in haematological malignancies but has very little effect in solid tumours.

- Where bisphosphonates are not available, hypercalcaemia may well indicate the terminal phase, as the patient becomes more drowsy, confused and dehydrated. In this situation simple measures like regular mouth care, nursing care such as bowel care and regular turning together with pain and symptom control can enable a dignified and comfortable death. (See section 5:5.11Practical Aspects of Pain Control: The Nurses Role)

Hypercalcaemia should not be considered in isolation. How active the treatment should be in an individual patient will depend on how distressing the symptoms are to the patient and whether any further treatment, of the malignancy, is available and likely to be of benefit.

9.3 COMING TOWARDS THE END:

"Watching the peaceful death of a human being, reminds us of a falling star, one of the millions of lights in a vast sky that flares up for a brief moment only to disappear into the endless night forever"[16]

The health worker or volunteer, who has supported the patient and family, will know when the end is near. Many families fear the time of death and need reassurance as to the signs of dying and what they need to be prepared for.

16 Kubler Ross E. (1969) On Death and Dying, Tavistock, London

Signs of Dying:

1. Gradual increase in drowsiness and/or weakness.

2. Changes in breathing pattern: Cheyne Stokes respiration may occur.

3. Skin colour changes as circulation changes.

4. Terminal restlessness may occur.

MANAGEMENT:

1. Medications: Review Medication and withdraw all non-essential medications.

Morphine dose can often be reduced in the face of drowsiness but should not be discontinued. It can be dropped into the mouth and absorbed from the buccal mucosa if the patient is unconscious or unable to swallow. If, due to the rapid reduction in renal clearance, signs of toxicity such as morphine twitches occur, then the morphine may need to be discontinued for some hours and then introduced at half the usual dose and given less frequently.

Anticonvulsants could be replaced with rectal diazepam if necessary.

Hyoscine hydrobromide can be given to relieve the death rattle. However this is rarely required, if it is explained to the relatives that it usually does not distress the patient.

Terminal restlessness can be a problem and causes such as distended bladder or other remedial physical discomforts need to be excluded. It can be controlled by haloperidol

2.5-5mg +- diazepam 5 mgs orally or midazolam 2.5mgs im which lasts about 3 hours.

2. Family Counselling: The presence of a loved one, holding hands, touching, praying etc can really calm the patient. The African custom of all the friends and family being around at the end, seems to comfort the patient and family, but can bring problems when they all have different ideas on management! The health worker and volunteer need to be calm and firm in defending the patients comfort and preventing management which can prevent peace at the end such as sudden admission to hospital.

3. The Holistic approach continues to the end of life and beyond. It is most important that the health worker keeps in touch with relatives throughout the illness, explaining procedures and reasons for treatments, answering questions, counselling and praying when necessary. Help from other team members or organisations should be sought when indicated.

Help for families left behind may be needed in the form of emotional or financial support. The team should be aware of facilities available in their District.

10. ANTIRETROVIRAL DRUGS (ARVs) IN END OF LIFE CARE:

SOME ETHICAL ISSUES:

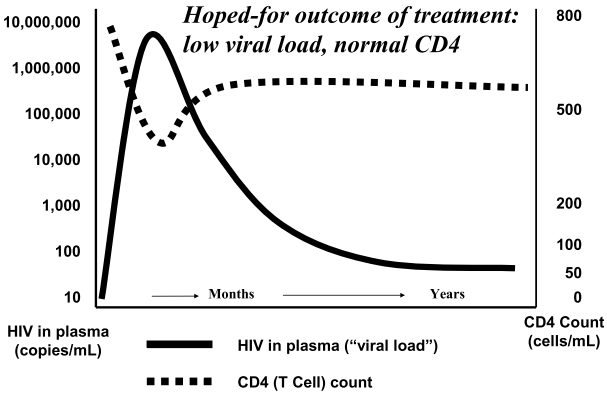


Figure 12: Role that ARVs play in the body's immunity.

The role of ARVs are to reduce viral load as much as possible for as long as possible, to allow immune reconstitution when CD4 counts increase, to halt disease progression & development of OIs and ultimately to prolong & improve the quality of life. The above fig represents the role that ARVs play in the body's immunity. (see also figures 2 and 14)

As the price of ARV's is reduced, more HIV patients will have access to these drugs. By March 2010 over 220,000 HIV positive patients were receiving HAART countrywide. Although this is a tremendous increase from

67,525 in 2005 owing to increased access through support from PEPFAR, the World Bank and Global Fund for AIDS, TB and malaria, it is estimated that over 400,000 patients need to be on HAART. Even then many more patients are now presenting to Hospice when already initiated on ARVs, particularly when there are failing their treatment. So we need to be ready for this with knowledge and expertise on co-managing AIDS and OIs. Patients are presenting differently and this has to be addressed. For this reason an extra section is included in this book on ARVs. (See Section III)

PALLIATIVE CARE AND ARV'S

Patients are now presenting to Hospice critically ill on ARVs. These drugs have side effects, which get worse as the body fails. Also the cost of the drugs and monitoring can deplete a resource strapped family of school fees and even food for the dependants. Ethical issues now are presenting to health workers.

With all medical decisions, the benefits and burdens must be explained to the patient and the relatives and they will make the decision, which must be respected by the health professional. However we must be informed. Many health professionals still have difficulty breaking bad news and are reluctant to explain to the patient or family, that these drugs are now no longer going to assist. So when should this be considered?

1. When the patient had permanent brain

damage. This usually means that there is psycho neurological damage, which has been present for more than 6 weeks.

2. When the side effects of the medications are destroying the quality of life of the patient and family attempts to keep to the timing of medications. (Switch to different ARVS may be considered in this situation.)

3. When life is short in the experience of the health professional and the family is being denied basic needs by the costs of the drugs.

These are new areas of decision making in end of life care and should be discussed more as these problems can only increase in the future and are specific for the third reason, in Africa and resource strapped countries.

11. SOME SPECIAL TREATMENTS IN TERMINAL CARE:

11.1 BLOOD TRANSFUSION

> A blood transfusion should not be given merely to treat low haemoglobin, or in the hope that it will make the patient feel better, or to help the doctor feel he is "doing something".

Chronic anaemia is common in the terminal stages of advanced cancer. Symptoms and

signs associated with anaemia include: (see box) but they are seldom significant unless the haemoglobin has fallen rapidly due to bleeding and the haemoglobin is below 4g/dl. The decision whether or not to transfuse is made more difficult by the facts that:

(a) Many patients fear transfusion in Africa due to HIV.

(b) Transfusion is not an option for a poor patient in the village.

(c) Many of the symptoms from the anaemia of chronic disease mimic those of the advanced cancer.

(d) Previous transfusions may have produced a placebo effect influencing the patient's view of its benefit.

(e) Normochromic normocytic anaemia of advanced cancers does not respond to oral haematinics, which can cause GI upset and increase constipation.

INDICATIONS FOR TRANSFUSION

1. Symptoms thought to be DIRECTLY due to the anaemia (and not the underlying cancer) eg from a massive haemorrhaging from a tumour, where the patient's activity is limited by the anaemia and where the haemoglobin is less than 4g/dl.

2. Unequivocal evidence of benefit from a previous transfusion.

11.2 ANTIBIOTICS IN TERMINAL CARE

A. AIDS:

It is often appropriate to treat infections in the AIDS patient as many life-threatening situations can be reversed to allow the patient to live longer with a good quality of life. The decision to introduce antibiotics depends on the stage of the disease weighed against the side effects of the drugs.

Although a list of present recommendations for antibiotic and antifungal treatment of opportunistic infections is given in appendix 6, we are aware that most patients in Africa cannot afford them. If they can afford them, the health workers role is to advise having considered the advantages for the patient against the side effects of the drug. Antibiotics need to be used rationally and appropriately to prevent the development of bacteria resistant to the drugs.

B. CANCER:

Antibiotics should be restricted in end of life situations to the following:

1. When there are good reasons for thinking that the patient's present symptoms are due to, or aggravated by, an easily treatable infection - for example, in chest or bladder.
2. When the treatment is not going to be more unpleasant for the patient than the symptoms themselves. They should not be used indiscriminately for patients with lung cancer suffering increasing cough and breathlessness but only where

infection is evident and treatable.

Similarly, urinary symptoms might well be due to local invasion of the bladder by a pelvic tumour or due to the presence of accumulating ascites.

The side effects of some antibiotics - oral thrush, nausea, diarrhoea, and secondary infection by resistant organisms - may be much more unpleasant and difficult to treat than the original infection.

Note: Pyrexia of unknown origin (PUO) is common in cancer and AIDS. African patients usually know their own symptoms of malaria and malaria must be treated. However fever may also be due to pyrogens from a tumour. This pyrexia does not respond to antibiotics. Naproxen 375mg bd has been shown to control the fever and prednisolone 15 mgs od improves appetite and well being.

11.3 STEROIDS IN TERMINAL CARE

Steroids have many uses in the management of the terminally ill and can prove very beneficial. However, caution must still be used and the dose reduced to the lowest effective maintenance dose as quickly as possible and the drug withdrawn if no benefit is obtained within one or two weeks. They are, in effect, a "life support" system and their benefits must constantly be weighed against their side effects. However most side effects occur with long term use and long term is not a feature in many of our own patients. Care must be taken in the AIDS patient as steroids further

decrease immunity. However when used in severely immuno-suppressed patients with very low CD4 counts, then scientifically there is nothing to be lost. If indicated they should be given together with an antifungal agent such as nystatin 500,000 units qid or ketoconazole 200mgs daily while being vigilant for the onset of candidiasis. Hospice Uganda has had very good results with short courses given in certain AIDS conditions, with improvement in pain, quality of life and even prolongation of life. Until further research is done, short courses only should be given (in patients with AIDS and cancer may require longer treatment with steroids for symptom control). Dosage use varies from unit to unit and from author to author. Because of this, the following table has been collated from the literature by Dr Nicky Bailhache, and compared them to doses used in our own Hospice experience here in Uganda.
Corticosteroids interact with anticonvulsants, (e.g. phenytoin when the dose of steroid needs to be doubled for the same effect), rifampicin which increases the metabolism of steroids. Steroids interact with anti-diabetic, anti-hypertensive medications and diuretics.

Consider steroids in AIDS for the following:
Raised intracranial pressure (CCM)
oesophageal ulceration
Mouth ulceration (topical application)
Stevens Johnson syndrome
Severe pruritis

dexamethasone 1mg = prednisolone 7mgs

prednisolone 1mg = 25mgs hydrocortisone

TABLE: RECOMMENDED INITIAL DOSES OF DEXAMETHASONE IN mgs.

CONDITION	WHO10	ROBERT TWYCROSS11	PETER KAYE12	BNF13	PCF2	HOSPICE UGANDA
Spinal cord compression	10-16	16-32	16		16	16-24
Raised intracranial pressure	8-16	8-16	16	16	8 – 16	16
Nerve compression	4-6		6-12	8 – 16		8
Intestinal obstruction	8-16		6-12	8 - 16		8
Oesophageal ulceration (HIV)				8		16
Bronchial obstruction	4-8		6-12	4-8		8
SVC compression			8-12			16
Tumour causing lymphoedema			4-8			8
Intractable nausea	10-20	8-20	8			8
Lymphangitis carcinomatosis	8		8			8
Anorexia/asthenia	2-4	2-4	2-4	2-4		2-4

10 WHO, 1998, Symptom relief in terminal illness

11 Twycross R. 1994, Pain Relief in Advanced Cancer, 1997, Symptom Management in Advanced Cancer, 1998,

12 Kaye P. 1994, A-Z of Hospice and Palliative Medicine, A-Z pocket book of symptom control

13 British National Formulary, BNF 46 - September 2003 I need to check the doses in the most recent editions of these publications to ensure this is up to date

14 PCF4 -Palliative Care Formulary 2011

SECTION III: ANTIRETROVIRAL THERAPY

SECTION III: ANTIRETROVIRAL THERAPY

This section is included because of the increasing availability of Highly active Antiretroviral Treatment (HAART) in Africa, and need for palliative care providers to understand the role of HAART in palliative care for HIV/AIDS patients and the interface between palliative care and HAART.

12.1 HIV/AIDS: THE NATURAL HISTORY OF DISEASE

The Acquired Immunodeficiency Syndrome (AIDS) was first described as a clinical entity in 1981 and the Human Immunodeficiency Virus (HIV) was identified as the causative organism in 1983. In 2008 nearly 25 million people were living with HIV in Sub Saharan Africa (SSA), with the annual number of new infections being 1.9million, and 1.4 million deaths[17]. By 2008 for Uganda 1.1 million people were HIV infected, the same number as during the peak of the epidemic in 1994. Although antiretroviral therapy (ART) coverage rose from 67 000 (2005) the number of persons needing but not receiving ART has only slightly decreased from 127 600 (2005) to 111 100 (2009) if the ART initiation

17 UNAIDS AIDS epidemic in Sub-Saharan Africa Fact sheet December 2009
http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf

criteria is a CD4 cell count <200[18]. If this is raised to <350 as it is being proposed, the estimated number of patients that need ART is >500,000. Many are currently receiving free drugs. Without treatment in rural Uganda median time from sero-conversion to death is 9.8 years, median time from WHO stage 4 HIV (AIDS) to death is 9.2 months[19].

Modes of Transmission

The major modes of acquiring HIV infection are:-

- Sexual Transmission: including via heterosexual and homosexual contact
- Parenteral Transmission: predominantly through accidental needle pricks. In Uganda, the Blood Transfusion services has tremendously reduced transmission through this route. Injection drug use and unscreened blood products is quite rare.
- Perinatal Transmission: from mother to child

The Virus

HIV belongs to the lentivirus (lenti meaning

18 AIDS 2008, 22:503–510

19 Morgan D. et al (2002) HIV infection in rural Africa is there a difference in median time to AIDS and survival compared with that in industrialised countries? *AIDS* 2002, 16: 597 – 603

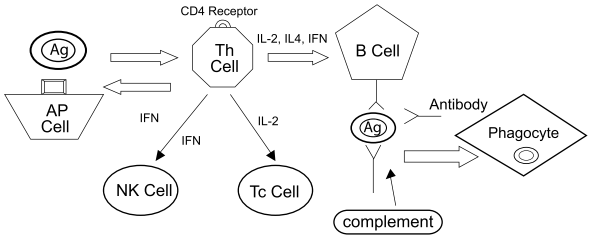
slow) group of the retrovirus family. There are at least 2 types of the virus. HIV-1 and HIV 2. HIV-2 is almost entirely confined to West Africa, although there is some evidence of its spread to the Indian Sub Continent.

Retroviruses carry their genetic material as RNA. This must be converted, by an enzyme called *reverse transcriptase,* into DNA, which is then inserted into the host or infected cells DNA, enabling the virus to then replicate.

HIV causes illness due to the direct effects of the virus attacking the body tissue and organs as well as due to the effects of the virus in destroying parts of the immune system.

The HIV virus when it enters the body recognises cells with a CD4 receptor on their surface, it infects these cells and ultimately destroys them.

The T helper cells, the commanders of the immune system army are cells with CD4 receptors on their surface. They are infected by and destroyed by HIV, thus HIV infection results in failure of the immune system to co ordinate the body's defence against infection (see figure 1).



Antigen (Ag) (foreign protein) is presented to T-helper cells (TH cells) by the Antigen presenting cell (AP Cell). T-helper cells are the commanders of the immune response secreting cytokine signals which coordinate the immune response to antigen.

Cytokines producced by the Th cells activate T-cytotoxic cells (Tc cells) to kill cells infected with intracellular organisms and viruses and Natural Killer cells (NK cells), which are involved in tumour surveillance. B lymphocytes (B cells) are activated to produce antibodies (AB) against the antigen when binds to antibodies on the B surface in the presence of cytokine signals produced by T-helper cells. Antibody then coats theantigen together with complement (opsonisation) and enables it to be ingested by phagocytes and destroyed.

Figure 13: Components of the Immune Response

12.2 CLINICAL FEATURES OF HIV INFECTION

Following exposure to HIV the usual onset of symptoms occurs

within 2 – 4 weeks but can be as long as 6 weeks.

Seroconversion / Primary HIV Infection

Most HIV seroconversion is asymptomatic, however in some patients it is a mild nonspecific illness that may occur 6 to 8 weeks after exposure, this is known as seroconversion illness / primary HIV infection. Symptoms may include, fever, joint pains, lethargy, lymphadenopathy, sore throat, mouth ulcers, a faint maculopapular skin rash (similar to measles rash) and commonly headache.

Meningoencephalitis and neuropathy have been reported but are said to be rare. This illness lasts about 2 – 3 weeks and recovery is usually complete.

During seroconversion illness the CD4 lymphocytes may be markedly depleted, at times so severe as to be associated with opportunistic infections such as pneumocystis carinii pneumonia and thrush. Antibodies to HIV at this early stage may be absent but levels of circulating virus and viral RNA (viral load) are usually high. The fall in CD4 cells is usually transient and the number usually increases again as the patient recovers from the seroconversion illness.

Over 95% of patients seroconvert to positive HIV serology within 6 months following exposure using standard serological HIV testing techniques, this is used for follow-up of established transmission events such as transfusion or needle stick injuries.

Clinical Latent Period

Most people with HIV infection are asymptomatic for a substantial though variable period of time. However the virus continues to replicate and people remain infectious. Patients generally have no findings on examination except for lymphadenopathy in some. Persistent Generalised Lymphadenopathy (PGL) is defined as having enlarged lymph nodes (> 1cm) at two or more sites excluding the inguinal nodes for more than 3 months in the absence of causes

other than HIV infection. These lymph nodes often contain high levels of HIV. Initially CD4 cell death and replacement are in near balance, thus a relatively steady state of cell counts and viral load may occur. However, as HIV infection progresses, the CD4 cell count falls and the body is less able to control HIV replication and so the levels of virus rise (see also figures 2 and 12).

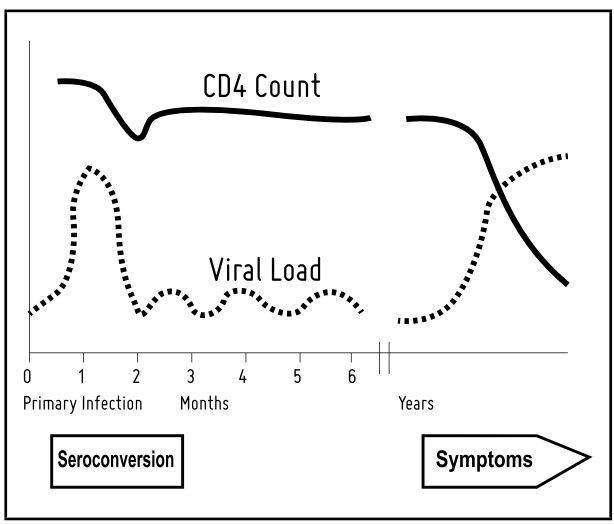


Figure 14: Natural history of HIV infection (cf fig 12)

Life expectancy for an HIV-infected patient without HAART is around 10 years. There are however treatment strategies known to prolong survival including septrin prophylaxis and HAART.

12.3 SYMPTOMATIC HIV INFECTION AND OPPORTUNISTIC

INFECTIONS

As the CD4 count falls and the immune system fails, the body is less able to mount a good immune response against both infections and some malignancies leading to the development of opportunistic infections and cancers. (see table below)

Many clinical episodes of HIV related disease represent reactivation of a previously acquired infection which has been latent, but the damaged immune system is no longer able to keep it in check. The patient encounters other infections, after they have been infected with HIV and may develop diseases related to these.

High-grade pathogens like Mycobacterium tuberculosis (TB), Candida and Herpes viruses may be clinically relevant even when immunosuppression is mild and will be encountered earlier in the course of the disease.

Less virulent organisms such as Cryptosporidium and Mycobacterium Avium Intracellularae (MAI) and Cryptococcus neoformens cause disease when a patient is severely immunocompromised.

CD4 Count cells / mm3	Infectious Complication	Non Infectious Complication
> 500	Seroconversion Vaginal Thrush	PGL, Myopathy, Guillian Barre Syndrome Aseptic Meningitis
200 – 500	Pneumonia bacterial Pulmonary TB Herpes Zoster Candidal Oesophagitis Kaposi's Sarcoma Oral Hairy Leukoplakia Acute Cryptosporidia diarrhoea – self limited	CIN / Carcinoma Cervix Non Hodgkins Lymphoma Hodgkins Disease Anaemia Idiopathic Thrombocytopenic Purpura (ITP) Lymphocytic Interstitial Pneumonitis (LIP) Mononeuritis Multiplex
<200	Pneumocystis Carinii Pneumonia (PCP), Dissem./ chronic Herpes Simplex, Toxoplasmosis, Progressive Multifocal Leukoencephalopathy (PML) Cryptococcosis, Milliary / Extrapulmonary TB, crypto/ microsporidia chronic diarrhoea Dissem. Histoplasmosis & Coccidioidomycosis	Wasting CNS lymphoma Cardiomyopathy Neuropathy HIV associated dementia
< 50	Disseminated CMV Dissem. Mycobacterium Avium Intracellularae (MAI)	

This hierarchy of infection is important as it provides opportunities to initiate appropriate interventions with prophylactic drugs and treatment.

WHO Clinical Staging of HIV/AIDS

The World Health Organisation has developed a clinical staging system for HIV infection and Disease.

Clinical stage 1 Asymptomatic

Persistent Generalised Lymphadenopathy

Performance scale 1 asymptomatic, normal activity

Clinical Stage 2

Weight Loss < 10% of body weight

Minor Cutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infection, recurrent oral ulcers, angular cheilitis)

Zoster within the last 5 years

Recurrent upper respiratory tract infections (bacterial sinusitis)

+/- Performance scale 2 symptomatic, but normal activity

Clinical Stage 3

Weight loss > 10%

Unexplained chronic diarrhoea > 1 month

Unexplained prolonged fever > 1 month

Oral candida (thrush)

Oral Hairy Leukoplakia (OHL)

Pulmonary TB within the past year*

Severe bacterial infection)* (pneumonia, pyomyositis)

+/- Performance scale 3 bedridden < 50% of the day during the last month

Clinical Stage 4

HIV wasting syndrome* (weight loss > 10%, plus either unexplained chronic diarrhoea >1 month or chronic weakness and unexplained prolonged fever >1 month)

Pneumocystis Carinii Pneumonia*

Toxoplasmosis Brain*

Cryptosporidiosis with diarrhoea > 1 month*

Isosporosis with diarrhoea > 1 month*

Cryptococcosis extra pulmonary*

CMV disease affecting an organ other than liver, spleen or lymph nodes*

Herpes virus infection > 1 month or visceral involvement*

Progressive Multifocal Leukoencephalopathy (PML)*

Disseminated Endemic Mycosis*

(histoplasmosis, coccidioidomycosis)

Candidiasis* (oesophageal, tracheal, bronchial, pulmonary)

Atypical Mycobacteriosis disseminated*

Non-typhoid Salmonella septicaemia*

Extra pulmonary TB*

Lymphoma*

Kaposi 's sarcoma*

HIV encephalopathy* (clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent condition other than HIV which could explain the findings.

+/- Performance scale 4 bedridden > 50% of the day during the past month

* AIDS Defining Diagnosis.

The median time from the onset of severe immunosuppression (defined as a CD4 count <200) to an AIDS defining illness in the West is 12 – 18 months in patients not receiving antiretroviral drugs. 10% of patients develop an AIDS defining diagnosis with a CD4 count > 200. Patients with Advanced HIV infection (defined as a CD4 count < 50) have a limited life expectancy with a median survival of 12 – 18 months. Most patients who die of HIV related complications have CD4 counts < 50. HIV has other targets in the body other than

the immune system and these can explain some of the other clinical sequelae of HIV infection such as peripheral neuropathy, pancreatitis, etc.

Infection of the central nervous system occurs at an early stage of HIV infection and can result in AIDS dementia complex, vacuolar myelopathy of the spinal cord and a sensory polyneuropathy affecting the hands and feet which can cause severe pain. HIV enteropathy is used to describe a syndrome of diarrhoea, malabsorption and weight loss for which no other explanation is found. Villous atrophy is a common histological finding and small bowel permeability is increased. HIV related cardiomyopathy and nephropathy have been described. Adrenal insufficiency also may occur.

Thus HIV is a multisystem disease. It is a major cause of morbidity and mortality worldwide and especially in Africa. HIV infection may be asymptomatic for a number of years whilst the virus insidiously damages the immune system. As the level of immunity falls patients become susceptible to specific types of infection. Many of these infections such as oesophageal candida, toxoplasmosis, tuberculosis, and pneumonia can be treated with inexpensive medications.

It is important to look for opportunistic infections as a cause of pain and symptoms in HIV positive patients, treating them may enable a patient to recover, stop analgesics and improve greatly even returning to work.

12.4 TREATMENT OF HIV INFECTION

General Advice

A balanced diet, and sufficient rest are basic requirements for health and important in a patient with HIV too.

Washing hands before eating anything, drinking boiled water and even cleaning teeth with boiled water are important in reducing diarrhoeal disease. Standard water treatment and chlorination do not kill cryptosporidium.

It has been shown that HIV positive patients have more frequent infections with malaria and higher parasitaemias than patients not infected with HIV[20] . It is therefore standard practice in many centres to recommend that HIV positive patients use insecticide treated bed-nets to try and reduce episodes of malaria.

Prophylaxis

Septrin prophylaxis (960mg od or three times weekly) is recommended by the WHO and the Joint United nation Programme on HIV / AIDS for HIV infected patients in Africa with symptomatic HIV infection (WHO stages 2,3 and 4) and for asymptomatic individuals with a CD4 count < 500 x 106 /l.

Septrin prophylaxis has been shown to reduce

20 French N et al (2001) Increasing rates of malarial fever with deteriorating immune status in HIV1 infected Ugandan Adults **AIDS 15**, 899 - 906

mortality and morbidity in these patients[2122] and is believed to protect against infections such as:- Salmonella septicaemia, isospora, cyclospora, toxoplasmosis, pneumococcal infection, pneumocystis carinii pneumonia, and malaria.

Alternatives to Septrin: Dapsone 100mg daily or 50mg twice daily, Atovaquone 750mg twice daily with food, Nebulized Pentamidine 300mg monthly, Dapsone 200mg weekly + pyrimethamine 75mg weekly + leucovorin 25mg weekly if these agents are available

NOTE:

1. *The above are effective at preventing PCP (and possibly toxoplasmosis) but do not provide the same broad cover against bacterial infections and malaria*

2. *While there is evidence that it is safe to stop Septrin in the West once a patient has enjoyed a good CD4 response to ART (i.e >200 cells/106/l), it is not yet clear when Septrin should be stopped in Africans, as the benefits of this prophylaxis are so broad.*

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21 Anglaret X. et al (1999) Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1 infected adults in Abidjan, Cote d'Ivoire: a randomised trial **Lancet 353,** 1463 - 1468

22 Badri M. et al (2001) Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa : an evaluation of the provisional WHO / UNAIDS recommendations **AIDS 15,** 1143 – 1148

Cryptococcosis

Secondary prophylaxis following treatment of cryptococcal meningitis (i.e. for those patients who have already had a single episode) is recommended with Fluconazole 100 - 200 mg daily The alternative is Itraconazole 200 mg daily.The role for primary prophylaxis has been explored since primary prevention would theoretically lessen the incidence of cryptococcal meningitis, a lethal OI.

A Cochrane Review by Chang L et al of 5 studies with 1,316 study patients most of whom had CD4 cell counts <150 cells/µl showed that with primary antifungal prophylaxis the incidence of cryptococcal disease was decreased compared to those taking placebo, but that there was no significant difference in overall mortality observed. This in effect undermines the use of antifungals as primary prophylaxis in AIDS patients, favouring clinician reviews for this OI.

http://www2.cochrane.org/reviews/en/ab004773.html

12.5 ANTIRETROVIRAL DRUGS

Antiretroviral drugs have had a dramatic effect on the course of HIV /AIDS, after their introduction in America in 1995 / 6 the rate of AIDS deaths fell by 12% in 1996, 44% in 1997 and 21% in 1998.

The biological rationale behind the use of antiretroviral drugs is to enable the sustained inhibition of viral replication, which enables

the partial reconstitution of the immune system in most patients, reducing the risk of opportunistic infections and reducing the progression of the disease. The reservoir of HIV within infected latent CD4 receptor positive T-helper cells prevents the eradication of the virus.

Thus antiretroviral treatment results at best in long-term suppression of the HIV virus but not a cure (It is important to explain this to patients some of whom have misunderstood terms like "undetectable viral load" to mean that they are cured of HIV).. HAART is currently a life-long treatment requiring good compliance to avoid resistance developing and failure of the regimen. Antiretroviral drugs can significantly delay progression of HIV infection to AIDS in many patients and return patients to good health.

There are many different antiretroviral drugs available, (28 individual or combination agents licensed for HIV treatment by March 2010) they target different points in the replication of HIV and therefore inhibit it. Antiretroviral drugs are used in combination, like the drugs used to treat tuberculosis, to try and prevent drug resistance developing. The replication of the HIV virus and targets for antiretroviral treatment are shown in figure 15.

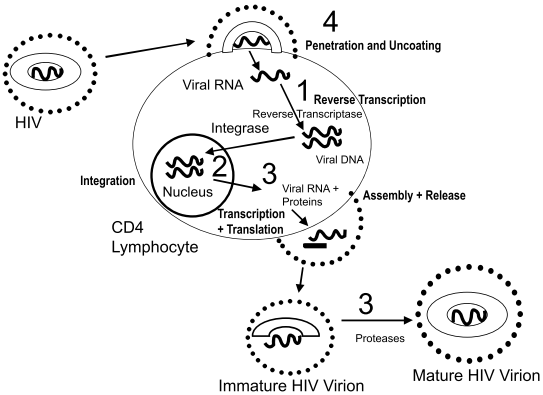

Figure 15: HIV life Cycle in a CD4 lymphocyte and Sites of Antiretroviral Action

HIV enters the CD 4 Lymphocyte via the CD4 receptor, it injects it's RNA into the cell, this is converted by a viral enzyme called reverse transcriptase into viral DNA which is then inserted or integrated into the host cells DNA by the enzyme integrase. This viral DNA in the host cell genome is then translated into RNA, this allows the production of viral proteins and a new generation of HIV virions, which are assembled in the cytoplasm of the cell and are then released. Once released, viral proteases act to allow the immature virions to mature and then become able to infect other cells. On releasing the virions the CD4 cell is destroyed thus depleting the immune system.

Targets for antiretroviral drugs are (**1)** Reverse transcriptase enzyme, (**2)** Integrase Enzyme, and (**3)** Protease Enzymes (**4**) Entry inhibitors.

There are currently 5 types of antiretroviral drugs used in the treatment of HIV these are:

12.5.1 Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

These are competitive inhibitors of the enzyme reverse transcriptase. They are nucleoside analogues, which mimic the building blocks of DNA, but when they are inserted by reverse transcriptase into the viral DNA strand it is synthesising, they prevent other nucleosides being added and therefore inhibit the insertion of viral DNA into the cell DNA and viral replication. Mutations in the viral Reverse transcriptase genes can reduce susceptibility to some NRTIs, promoting drug resistance.

12.5.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

These drugs bind to the reverse transcriptase enzyme at a different site from its active site but cause the active site to change in shape, stopping nucleosides entering and preventing enzyme activity. HIV can become resistant to NNRTIs

12.5.3 Protease Inhibitors (PIs)

Competitively bind to the substrate site of viral proteases inhibiting the production of viral proteins necessary for the release and development of mature HIV virions. Resistance and cross-resistance to different PIs can occur.

12.5.4 Entry Inhibitors

Maraviroc, a synthetic peptide, specifically blocks the **chemokine** receptor **CCR5** which HIV uses as a coreceptor to bind and enter a human **macrophage**. It therefore inhibits HIV from binding with the CD4 cell membrane. This drug is currently only used in some expert centres for salvage treatment when all other drugs have failed.

12.5.5 Fusion Inhibitors:

Enfuvirtide, the first of a novel class of antiretroviral drugs used in combination therapy for the treatment of HIV-1 infection, works by disrupting the HIV-1 molecular machinery at the final stage of fusion with the target cell, preventing uninfected cells from becoming infected. A biomimetic peptide, enfuvirtide was designed to mimic components of the HIV-1 fusion machinery and displace them, preventing normal fusion.

12.5.6 Integrase Inhibitors

Raltegravir is an integrase enzyme inhibitor that prevents the incorporation of the transformed RNA into the host cell DNA. It is a new drug, licensed in December 2007 but has a lot of potentials.

12.5.7 MANAGING ANTIRETROVIRAL REGIME

HAART is a lifelong treatment, compliance is vital for its efficacy and to avoid resistance and failure of the regimen. When starting a

patient on antiretroviral drugs it is important to consider:

- The patient's stage of disease and risk of progression to AIDS
- The cost of treatment and monitoring
- The patient's motivation to comply with treatment
- The side effects of treatment
- The possibility of drug resistance
- Likely drug interactions
- The logistics of taking the drugs correctly
- The likely efficacy of the antiretroviral regime
- The possibility of an underlying untreated opportunistic infection and risk of Immune Reconstitution Syndrome (IRIS)

1. The Patient's stage of Disease and risk of Progression to AIDS

There are clear indications for starting antiretroviral treatment in patients with symptomatic HIV infection, and patients with asymptomatic infection but with CD4 counts < 250/mm3. (Soon Uganda is likely to recommend initiation of ART at CD4 counts <350/mm3) A high viral load (amount of virus in the blood) is associated with more rapid progression of HIV disease to AIDS. Thus some experts recommend starting

ART for patients with a viral load >30,000 copies/mm3 at any stage of disease and CD4 cell count.. It is important to follow your country guidelines for the initiation of HAART and management of AIDS in patients. These may change over time with progress made in research, drug development and the experiences of patient care.

2. The Cost of Treatment

With recent WHO and Global fund initiatives antiretroviral drugs are becoming increasingly available. Many centres have access to free drugs for many patients and costs of drugs for other patients have reduced. There are however hidden costs even in accessing free drugs, patients must attend regularly to collect drugs and be reviewed incurring transport costs and some tests for monitoring the effectiveness of treatment eg. CD4 counts may need to be paid for and can be costly. Compliance is vital to avoid resistance developing and for HAART to be effective therefore these issues should be discussed before commencing treatment

3. The Patient's Motivation to Comply with Treatment

Antiretroviral drugs have side effects. Their effective administration to enable adequate absorption may involve taking drugs 1 or 2 hours before or after meals. Patients may need to change meal times and food habits to fit their drug regimes. Non-compliance even for a short time may result in rapid rebound of

the virus levels and disease progression and also encourage drug resistance to develop. A patient should therefore be counselled carefully before starting antiretroviral treatment and be thoroughly motivated to continue it.

4. *Side effects and interactions*

Antiretroviral drugs have many important interactions and side effects (see table). Side effects are a major reason for patients stopping to take the drugs. Efaverenz should be avoided if there is a risk of pregnancy as it may be teratogenic.

It is important to consider possible interactions before prescribing any drug to patients on ART. Therapeutic drug monitoring is largely unavailable, and drug interactions can be unpredictable therefore it is important to be mindful of and check for interactions prior to initiating medications in patients on ART. A useful website is www.hiv-druginteractions.org.

A palliative care provider can potentially inactivate a patient's ART and promote resistance developing or increase the toxicity of the ART regimen through prescribing a medication that interacts with a patients ART regimen. If in doubt all drugs started in a patient on ART should be checked for interactions. Particular drugs to avoid in a palliative care setting are Phenytoin, Carbamazepine, Ketoconazole, Cimetidine, and Omeprazole.

DRUG	DOSE REGIME	SIDE EFFECTS	INTERACTIONS/ OTHER
1. Nucleoside Reverse Transcriptase Inhibitors NRTIs		Mitochondrial toxicity including Lactic acidosis Hepatic Steatosis Lipoatrophy	
Zidovudine (ZDV) AZT Retrovir*	300mg bd	As for NRTIs and :-Myelo-suppression, MCV > 100 Nausea, vomiting Myopathy, myalgia, Headaches, insomnia, nail pigmentation	Avoid using with chemotherapy as high risk of anaemia. Potentially increased risk of anemia with cotrimoxazole and dapsone
Stavudine (D4T) Zerit* (It is being phased out because of its toxicity)	30mg bd	As for NRTIs and :- Peripheral Neuropathy (motor and sensory) Hepatitis	Dose reduction if renal failure. Avoid administering with dapsone. Additive neuropathy with isoniazid in TB medicine.
Didanosine (DDI) Videx*	200mg bd or 400mg od 30mins before or 2 hrs after a meal	As for NRTIs and :Pancreatitis (avoid if PMH pancreatitis or alcohol +) Dry mouth, hyperuricaemia peripheral neuropathy, GI upset.	Dose reduction if renal failure. Avoid administering with dapsone. Additive neuropathy with isoniazid in TB medicine.

DRUG	DOSE REGIME	SIDE EFFECTS	INTERACTIONS/ OTHER
Lamivudine (3TC) Epivir*	150mg bd	As for NRTIs Few side effects none noted in drug trials. Paediatric case of pancreatitis reported	Dose reduction if renal failure
Tenofovir (TVF) Viread*	245mg od	Renal dysfunction/ failure	Interaction with DDI; reduce dose of DDI. Avoid if renal failure. Avoid amphotericin, acyclovir and aminogylcoside co-administration.
Emtricitabine (FTC)	200mg od		Once day dosing and well tolerated
Abacivir (ABC) Ziagen*	300mg bd	As for NRTIs and :- Hypersensitivity – DO NOT rechallenge as death likley Nausea	Very expensive

DRUG	DOSE REGIME	SIDE EFFECTS	INTERACTIONS/ OTHER
2. Non Nucleoside Reverse Transcripitase Inhibitors (NNRTI's)		Cutaneous (including Steven Johnson's) and hepatic (acute hepatitis) hypersensitivity reactions	Metabolised by cytochrome P450 Enzyme inducers reduce serum levels eg. Phenytoin, sulphonyl ureas, alcohol, carbemazepine, barbiturates, rifampicin Enzyme inhibitors may cause toxicity eg. Omeprazole, ethanol, isoniazid, cimetidine, ethambutol, fluconazole, ketoconazole)
Nevirapine (NVP) Viramune*	200mg bd Start with dose of 200mg od 14/7 to reduce side effects	Rash – maculopapular +/ itch (reduce starting dose to reduce risk) Steven Johnson Syndrome Hepatitis Nausea, Headache, Fever	Interaction with rifampicin - avoid if possible
Efavirenz (EFV) Stocrin* / Sustava*	600mg nocte avoid high fat meals	Rash, dysphoria, mood changes, dreams, insomnia, inc. cholesterol May be teratogenic	Can be used with Rifampicin
Etravirine (ETV, Intelence)	800mg twice a day		Should be taken with a meal

DRUG	DOSE REGIME	SIDE EFFECTS	INTERACTIONS/ OTHER
3. Protease Inhibitors	Complex regime	SE in 30 – 60% at 2 years Lipo-dystrophy (fat redistribution) Hyperlipidae-mia, Hypercho-lestrolaemia Diabetes Mellitus	Metabolised by cytochrome P450. Enzyme inducers reduce serum levels eg. Phenytoin, sulphonyl ureas, alcohol, carbemazepine, barbiturates, rifampicin Enzyme inhibitors may cause toxicity eg.Omeprazole, ethanol, isoniazid, cimetidine, ethambutol, fluconazole, ketoconazole Most PI's are now given with small dose of Ritonavir (eg 100mg bd). This boosts the levels of the active drugs and makes the PI more effective ('Boosted PI's')
Lopinavir with Ritonavir (comes as 'Kaletra')	3 tabs bd after food	As for PIs and : Diarrhoea	Must be stored at less than 25'c. If no fridge place pill bottle in sealed plastic bag and place this in a pot containing wet sand. Keep in shade in dwelling.
Saquinavir (SQV) Invirase* (hard gel) Fortovase* (soft gel)	1000mg bd *with Ritonavir 100mg bd* after food	As for PIs and : Abdominal discomfort Nausea	

DRUG	DOSE REGIME	SIDE EFFECTS	INTERACTIONS/ OTHER
Indinavir (IDV) Crixivan*	800mg bd *with Ritonavir 100mg bd*	As for PIs and :-Hyperbilirubinaemia (10%) Nephrolithiasis Nail changes Dry skin	Should aim for high fluid intake Avoid if renal failure.
Amprenavir (APV) Agenerase*	600mg bd *with Ritonavir 100mg bd*	As for PIs and :- Rash, nausea, diarrhoea	
Nelfinavir (NFV) Viracept*	750mg 8 hourly or 1250mg bd with food	As for PIs and :- Diarrhoea – mild / moderate Rash	NOTE: boosting with Ritonavir not effective

5. *Baseline investigations prior to starting ART.*

Many antiretroviral drugs are excreted via the liver or renal system therefore it is useful (but not essential) to check liver and renal function before starting ART, as the dose may need to be changed. Side effects of ARVs include hepatitis and bone marrow suppression therefore liver function tests and haemograms are helpful in monitoring for treatment toxicity.

Due to the interaction of many ARVs with TB drugs (see later) it is also important to rule out coexisting TB in patients, prior to starting ART. Often a CXR is required. HIV co-infection with hepatitis is also common, so exclusion of hepatitis viral infection, if possible, is also a good idea.

12.5.8 Initial Antiretroviral Regime

Because of cross-resistance between different antiretroviral drugs the first regime represents the patients' best chance of long-term viral control. Compliance is critical therefore the cost, the complexity of the regime and side effects are important considerations. First line regimens usually include a NNRTI with 2 NRTI's (for example Nevirapine, Lamivuidine and Stavudine **or** Efavirenz, Lamivuidne and Zidovudine). Combinations containing a protease inhibitor are often second line regimens.

12.5.9 Monitoring Response to Treatment

Blood tests can be used to monitor the effectiveness of HAART. The Viral load (VL) measures the amount of virus in the blood. The aim of HAART is an undetectable VL (< 50 copies/ mm3). The VL can rise transiently but significantly during an acute illness, therefore it should not be measured within 1 month of such events. When using VL to monitor response to HAART the expectation of successful treatment is an undetectable VL at 4 to 6 months. If a patient's viral load becomes detectable (or fails to become undetectable) this may mean the patient is not taking their drugs properly, has developed resistance or both. HIV infection results in immune system failure with progressive depletion of T helper or 'CD4' cells. The CD4 count should increase with treatment success and also falls with treatment failure.

In developing countries using the viral load to monitor treatment response is not possible in many patients due to cost. However, CD4 counts costs are becoming cheaper more accessible even though it is mainly in urban areas. Clinical indicators of effective treatment include weight gain and a reduction in the frequency and or severity of opportunistic infections. The CD4 count and immune system recovery may take many months to improve and usually lags behind the response of the viral load. An increase in the total lymphocyte count may be a pointer to increasing CD4 count. Clinical markers and other less expensive tests for following response to ART are currently being developed in Sub-Saharan Africa.

12.5.10 When to change Antiretroviral Regimes

There are 4 indications for changing the antiretroviral regime

- Toxicity
- Treatment failure
- Inability to comply with complex dosing regimes
- Cost

Antiretroviral drugs are complex particularly with regard to the development of drug resistance. If a palliative care provider believes that a patient is developing side effects from their regimen which cannot

be managed and necessitate changing the regimen or feels that a patient may be failing their ART regimen if they are deteriorating or developing new opportunistic infections, they should refer the patient back to their ART provider for further review and evaluation.

Changing ART regimen may have cost implications for the patient.

Examples of adverse drug events which may cause clinician to consider changing regimen include:

Severe peripheral neuropathy pain - (d4T, ddC, ddI)

Severe anaemia – AZT

Severe diarrhoea, despite loperamide after many weeks

Severe allergies involving mucous membranes, fever- NNRTIs, Abacavir

Pancreatitis- e.g. ddI, D4T

Hepatotoxicity/jaundice- Nevirapine, Ritonavir

Psychosis- Efavirenz

12.5.11 Tuberculosis Treatment and ART

It is estimated that worldwide one third of TB patients are co-infected with HIV. The HIV sero-prevalence among TB patient in Africa

is higher, up to 50-70% in some hospitals[23].

A reduced CD4 count promotes reactivation of and re-infection with Tuberculosis. Active tuberculosis up regulates HIV replication and speeds disease progression. TB is the leading cause of death in HIV patients worldwide. TB treatment consists of a multi drug regime including: - rifampicin, ethambutol, isoniazid, pyrazinamide and streptomycin. Rifampicin is a cP450 inducer, which therefore accelerates the metabolism of most NNRTIs eg. Nevirapine and PIs reducing drug levels and promoting the development of drug resistance to these ARVs.

It is now recommended that any HIV infected patient with active TB should be started on ART irrespective of the CD4 count. Until recently it was suggested if possible ART should be delayed until rifampicin treatment had finished or that rifambutin was substituted for rifampicin as it had less marked induction of cP450. Rifambutin use is limited by cost. Recent advice has changed. Essentially now the concurrent use of rifampicin and certain ARV regimes including Efavirenz based is possible. However TB should be excluded in patients before starting the initial ART regimen, and TB drugs should only be started in a patient on ART in conjunction with their ART provider.

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23 World Health Organization. A deadly partnership. Tuberculosis in the era of HIV. Global Tuberculosis Programme, World Health Organization Publication (Geneva), WHO/TB/96. 204

12.5.12 Immune Reconstitution Syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) is a condition of increasing importance and seen with increasing frequency as more patients access HAART. The effect of the antiretroviral drugs allows suppression of the virus and recovery of the immune system. In patients with underlying opportunistic infections such as Tuberculosis, Cryptococcal meningitis, toxoplasmosis, the immune system suddenly recovers enough to start fighting these underlying, previously hidden infections and mounts an immune response against them. This response can be quite violent and occurs classically within 3 – 8 weeks (but may be delayed for months) of a patient starting ART. Patients become acutely unwell, presenting with severe symptoms of infections, e.g. rapidly enlarging lymph nodes due to TB, rapidly developing signs of a mass lesion due to toxoplasmosis or TB, or other symptoms of opportunistic infections. Kaposi sarcoma IRIS has also now been described, and nearly insignificant skin and mucosal lesions can rapidly fungate or cause disfigurement. IRIS can be life threatening and requires management in conjunction with the ART provider. Patients require treatment of the opportunistic infection and often steroids to transiently dampen down the severity of the immune response. IRIS is an important consideration in a patient who deteriorates soon after starting HAART.

12.6 ARV PROTECTION FOR THOSE WORKING WITH HIV/AIDS PATIENTS

It is most important that we are prepared to protect health workers from needle stick injury when working with end of life care and critical illness. These are not common injuries but some have already died from the disease because not adequately protected.

The most important protection is to observe universal precautions like wearing gloves, protective clothes if available, and being always careful during procedures and disposal of needles and other sharps. In the event of a needle stick injury squeeze to make the injury bleed and wash with water or a detergent like chlorhexidine if available. Wash eyes and skin / mucous membranes with water if contaminated. Ideally take the first dose of a multiple ART regimen within an hour of the injury. The person then must present themselves as soon a possible to a health professionals or doctor who will decide whether this situation is low risk or High risk. If high risk they may continue the ART regimen for 1 month according to local protocols. Palliative care providers should ascertain local availability of post exposure prophylaxis regimens and determine a best locally available combination and clear path of access / policy for staff who sustain such an injury.

12.7 CONCLUSIONS

Antiretroviral drugs have fallen in cost and become increasingly available to more and more patients living with HIV. Costs are associated with ART and it is not without significant side effects, but it has been shown to significantly delay the progression of HIV infection to AIDS and transform the lives of many patients. HAART is not curative as reservoirs of virus still persist in spite of one having no detectable virus in the blood.

The cost of antiretroviral treatment is more than just the drugs. To be used effectively patients need to be monitored both for toxicity and response to treatment. For the best chance of effect, compliance is vital, therefore it is essential that patients are counselled before starting antiretrovirals and the regime most likely to promote compliance is the one started. In practice for most patients this is the cheapest regime.

ARVs have significant side effects, which can significantly reduce quality of life, and important drug interactions, which can effect metabolism and promote toxicity or drug resistance. The interactions with TB treatment and key palliative care drugs are particularly important.

Drug resistance is a major problem the likelihood of resistance occurring is increased with non- compliance particularly if one or two drugs are stopped and others continued.

It is important that all health professionals

have an understanding of ARVs, how they work, what ART involves, the importance of compliance, the interactions and side effects. They are then able to counsel patients about their treatment, be realistic about the future, weigh up the costs versus benefits of treatment for each individual refer appropriate patients for ART when available and not prescribe in ignorance a drug which may jeopardise the effectiveness of that treatment through interactions.

Palliative Care is still needed in the era of Antiretrovirals for patients with pain and symptoms related to the virus or treatment, for patients with HIV-related cancer, for patients who present too late for ART to be effective, for patients in whom available regimens fail and for those patients unable to access ART.

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Grant A., Katabira E. T., Marum L. H., De Cock K. (2004) HIV / Aids in Principles of Medicine in Africa Parry E. H. O., Godfrey R., Mabey D., Gill G., (3rd Edn), Cambridge University Press, Cambridge

WHO (2002) Scaling up antiretroviral therapy in resource-limited settings (available from www.unaids.org)

WHO (2003) Use of Antiretroviral Treatments in Adults (with particular reference to resource limited settings) WHO, Geneva

http://data.unaids.org/pub/Report/2010/uganda_2010_country_progress_report_en.pdf

Mwebesa E, Mpanga LS, Nakwagala F (2009) The Prevalence and factors associated with hypercalcemia among breast cancer patients in Mulago Hospital, Uganda. A dissertation for research project for MMed-Makerere University.

FURTHER INFORMATION AND REFERENCE MATERIAL

World Health Organisation (WHO)

Email to place orders: bookorders@who.int

Email queries to : publications@who.int

Useful WHO Publications Include:-

WHO ART Therapy – Web version June 2010

Cancer Pain Relief 2nd Edition WHO Geneva 1996

Symptom relief in Terminal Illness WHO Geneva 1998

Halley Stewart Library, St Christopher's Hospice

Tel: +44 (0)20 8768 4660 Fax: +44 (0)20 8776 9345

Email: d.brady@stchristophers.org.uk
Website: www.stchristophers.org.uk

PPSG Pain policy website (www.medsch.wisc.edu/painpolicy)

www.pallcare.info

USEFUL BOOKS

Palliative care training manual for health professionals,

Hospice Africa (Uganda.)

Price 15US$

Contact: Resource Centre, Hospice Africa (Uganda)

Email: info@hospicafrica.or.ug

Symptom Management Algorithms: A Handbook for Palliative Care

Linda Wrede-Seaman, MD. 2nd edition: 1999, ISBN: 188841107-4

Symptom Management in Advanced Cancer Twycross R., Wilcox A., 3rd Edition 2001 Radcliffe Medical Press ISBN 1 85775 510 3

Oxford Textbook of Palliative Medicine

Fourth Edition: Edited by Geoffrey Hanks, Nathan I. Cherny, Nicholas A. Christakis, Marie Fallon, Stein Kaasa and Russell K. Portenoy ISBN13: 9780199693146ISBN10: 0199693145 Paperback, 1704 pages Oct 2011

Palliative Care: A handbook for Palliative Care in Africa by the African Palliative Care Association (APCA), 2010.

Beating Pain: A pocket guide for Pain management in Africa. APCA, 2010.

A Guide to Symptom Relief in Palliative Care Regnard C., Hockley J., 5th Edition 2004 Radcliffe Medical Press ISBN 1 85775 930 3

JOURNALS PALLIATIVE CARE

The APCA Journal of Palliative Care.
Email: info@apca.co.ug

The Journal of Palliative Care Association of Uganda
Email: pcau@apca.co.ug

Innovations in End-of-Life Care (free on-line peer-reviewed journal): www2.edc.org/lastacts/ .

HIV / AIDS PALLIATIVE CARE

We miss you all: Kaleeba N. a personal testimony of AIDS and the beginnings of TASO.

HIV/AIDS CLINICAL CARE

HIVInfection, Diagnostic and Treatment Strategies for Health Care Workers, Katabira ET, Kamya MR, Mubiru FX, Bakyaita NN, 2000, second edition, STD/AIDS Control Programme. Ministry of Health, Republic of Uganda

HealthNet News - Community Health -A monthly publication featuring current, thematic public health information. A full-text version is distributed monthly.

Use of Antiretroviral Treatments in Adults (with particular reference to resource limited settings) **WHO Geneva 2000**

Scaling up antiretroviral therapy in resource-limited settings **WHO Geneva 2003 revision available from www.unaids.org**

A Clinical Guide to Supportive and Palliative Care, for HIV/AIDS in Sub-Saharan Africa 2006: Gwyther L, Merriman A, Mpang Sebuyira L, Scheitinger H:

PAEDIATRIC PALLIATIVE CARE

Cancer Pain Relief and Palliative Care in Children, WHO Geneva , 1998

PHARMACOLOGICAL INFORMATION

British National Formulary published by the BMA / British Pharmaceutical Association www.bnf.org available at a reduced cost from TALC and free access for resource poor countries on www.healthinternetwork.net

www.palliativedrugs.com Essential international independent information for health professionals about the use of drugs in palliative care. Bulletin board – able to ask questions re: difficult cases/use of drugs etc.

Palliative Care formulary Twycross R., Wilcock A., Charlesworth S., Dickman A., 2nd Edition 2002 Radcliffe Medical Press ISBN 1 85775 511 1

Other useful websites:

Pallimed blog: www.pallimed.org

American Pain Society: www.ampainsoc.org

Palliative Care Network: www.palliativecarenetwork.org

AIDS Drug Guidelines: http://aidsinfo.nih.gov/guidelines/

HIV Drug interations: www.hiv-druginteractions.org

The Initiative for Pediatric Palliative Care: www.ippcweb.org

Education in Palliative and End-of-Life Care: www.epec.net

Palliative care drugs: www.palliativedrugs.com

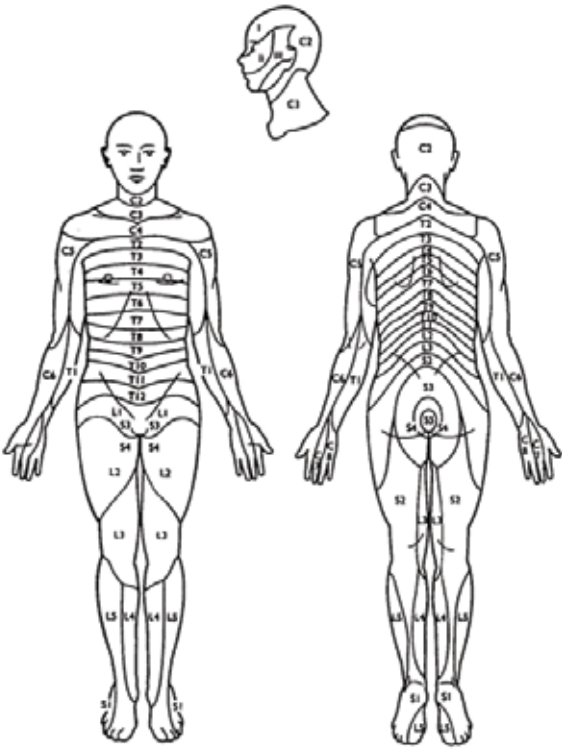
International Palliative Care Research Center: www.ipcrc.net

These and other books and Palliative Care journals are available for

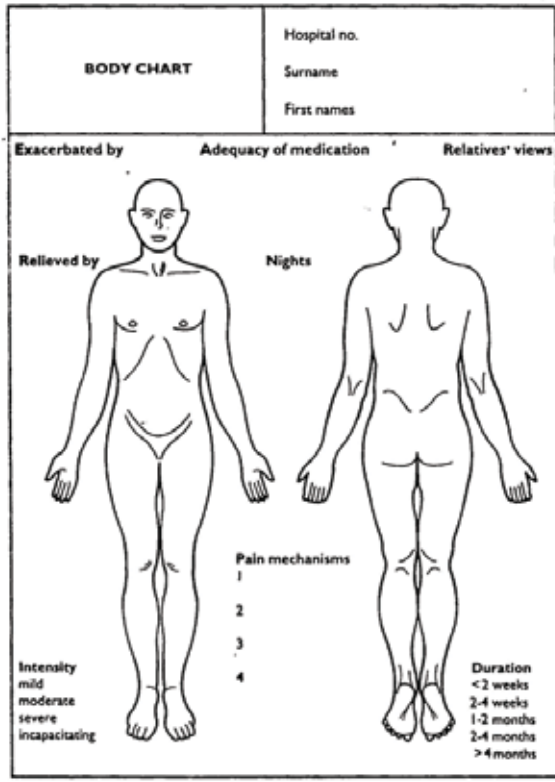
reference at Hospice Africa Uganda in Makindye, Kampala.

APPENDICES

Appendix 1: BODY CHARTS



Body Chart showing dermatomes, i.e. areas in which pain is experiences if the corresponding nerve is compressed or damaged.



Overprinted body chart used at Sobeli House for recording pain data

These Charts are given for quick reference. Full assessment of pain in included in the Hospice Africa record sheet.

Appendix 2 : Instructions for writing a prescription for Oral Morphine

Prescription must be written in own handwriting, including name and address or identifiation number of patient.
All figures must be also written in words.
Eg MORPHINE 5mg/5ml
Signify 10mg 4 hourly and 20mg at night.
Send 500mls

Hospice Uganda,
P.O.B 7757,
Kampala
20/4/02

Nassoke Christine,
No 1435, aged 14 yrs.
Rx morphine liquid 5 (five) mgs PER 5 (five) mls.
Signify 5 (five) mls 4 (four) hrly and
10 (ten) mls at night.
Quantity 500 (five hundred) mls.

Signature: Dr. G. Ddungu.
Official stamp:

for ORAL MORPHINE 50mg/5ml, MST tablets and morphine for injection.

Hospice Uganda
P.O.Box 7757,
Kampala
20/4/02

Kagwa Kizito,
aged 32 yrs
No 1395

MST (slow release morphine tabs) 30 (thirty)
mgs 12 (twelve) hrly
Quantity 14 (fourteen) tablets.

Dr. G. Ddungu

Dispenser at Hospice Africa Uganda, preparing oral morphine, 5mgs per 5 mls, from morphine powder.

This costs US$1.5 for 500 mls: enough for the average patient to be pain free for 10 days.

Public/Private/NGO partnerships have allowed morphine to be prepared centrally in Uganda. These partnerships can move forward the availability of morphine in a country.

Appendix 3:[24] MORPHINE SOLUTION FORMULAE

FORMULA FOR ORAL MORPHINE SOLUTION

5MG/5ML *using bronopol*

HOSPICE AFRICA, UGANDA PHARMACY DEPARTMENT

Batch No: _____ Date of mfg: _____ Exp date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Morphine sulphate powder BP			5g		
Bronopol BP crystal			1g		
Green Food Colour			0.4g		
Freshly boiled, cooled, water*	N/A	N/A	To 5000ml		

Procedure:

Tare the balance.

Weigh the morphine powder (calculated to scale) per batch size.

Transfer adequate purified water to a clean container (less than final volume)

Gently transfer the weighed powder to the water above and stir to dissolve.

24 From JMS Kampala and used in HAU pharmacy 2011

Filter and transfer the solution into a calibrated measuring jug.

Weigh Bronopol crystal 1g (calculated to scale)

Gently add it to the morphine solution while stirring to dissolve.

Weigh 0.4 g of green food colour add colour calculated to scale and add to above solution stir to dissolve.

Transfer to final container and make to final volume with purified water and stir.

Pack in to freshly washed containers.(Per procedure for washing packing containers)

Check the final product.

Label accordingly.

Expiry Date:

6-12 months from the date of manufacture. (Expiry date under observation and to date 10 months)

Storage conditions:

Store in a cool, dark place.

Label prepared by: _____

Final product checked by: _____

**We have used freshly boiled water for 17 years without mishap. Now using bottled water from a reliable and tested manufacturer. However ideally ionised or distilled water is preferable.*

FORMULA FOR ORAL MORPHINE SOLUTION

50MG/5ML *using bronopol*

HOSPICE AFRICA, UGANDA PHARMACY DEPARTMENT

Batch No: _____ Date of mfg: _____ Exp date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Morphine sulphate powder BP			50g		
Bronopol BP crystal			1g		
Red/Pink Food colour			0.4g		
Rwenzori water.	N/A	N/A	To 5000ml		

Procedure:

As above for 5mgs per 5 mls solution

FORMULA FOR ORAL MORPHINE SOLUTION

100MG/5ML *using bronopol*

HOSPICE AFRICA, UGANDA PHARMACY DEPARTMENT

Batch No: _____ Date of mfg: _____ Exp date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Morphine sulphate powder BP			20g		
Bronopol BP crystal			1g		
Blue Food colour			0.1g		
Pure water or deionised water	N/A	N/A	To 1000ml		

- Please note that it is recommended that all countries in Africa adopt these safe concentrations and using the same colour codes. This is because patients often cross borders and receive morphine from different countries. Doctors must be aware of the concentrations available in Africa and write the concentration on the prescription.
- Also note that the stronger concentrations should be made up in smaller amounts according to the needs of the patient. Green morphine is usually dispensed in 500ml bottles, pink in 250 ml bottles and blue in 40-100ml bottles according to the dose being given and the need for a supply to cover until next seen including break through doses.

Preservative recommended at present is Bronopol which has up to 8 months shelf life. Parabene has a shelf life of 3 months and may be used when bronopol is not available but it is also more expensive.

ALTERNATE FORMULAE FOR MAKING ORAL MORPHINE FROM POWDER using PARABENE[25]

1. Morphine Solution for Oral Use 50mg in 5mls (for storage for dilution and therefore colourless)

Batch No: _____ Date of mfg: _____ Exp date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Morphine sulphate powder BP			50g		
Parabene[11] concentrate			50ml		
Freshly boiled, cooled, water	N/A	N/A	To 5000ml		

Method:

Tare the balance.

Weigh the morphine powder and transfer into a clean bucket.

Make a paste by adding a small amount of water.

Gradually add water to approximately ¾ of

25 Parebene comes as powder: to be made up to a solution (see Pharmacopoeia) or as below:

the final volume.

Transfer the solution into a calibrated measuring jug.

Measure the parabene concentrate and gradually add it to the morphine solution whilst stirring, until fully dissolved. (**NB**: Parabene is poorly soluble in water; at least ¾ of the final volume of solution is needed to dissolve the parabene.)

If the solution is to be used for dispensing add 5 drops of red food colouring and stir thoroughly. Otherwise leave the solution colourless.

Make up to final volume with water and stir thoroughly.

Check the final product.

Transfer into a suitable clean container (5l jerry can) and label (see sample label below).

Sample label:

Expiry Date: 3 months from the date of manufacture.

Storage conditions: Store in a cool, dark place.

Label prepared by: _____

Final product checked by: _____

As this is a storage solution for smaller pharmacies then it can be diluted to strength of 5 mgs per 5 ml and green colour added. When giving as (50mgs per 5 ml) then is should be coloured pink.

2. FORMULA FOR ORAL MORPHINE SOLUTION 5mg in 5ml

Batch No: _____ Date of mfg: _____ Exp date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Oral morphine solution 50mg in 5ml (colourless)			500ml		
Parabene concentrate			45ml		
Freshly boiled, cooled, water	N/A	N/A	To 5000ml		
Green food colouring	N/A	N/A	0.2g		

FORMULA FOR PARABENE CONCENTRATE SOLUTION

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Methyl Parabene			480g		
Propyl Parabene			120g		
Propylene glycol	N/A	N/A	To 4000ml		

Method:

Tare the balance.

Weigh the Methyl Parabene and Propyl Parabene separately, and then transfer them in to one clean container.

Make a paste by adding a small amount of Propylene Glycol.

Gradually add to approximately final volume.

Transfer the solution into a calibrated measuring jug, gradually add Propylene Glycol into the solution whilst stirring, until fully dissolved.

Make up to final volume of 4000ml with Propylene Glycol and stir thoroughly.

Check the final product.

Transfer into a suitable clean container (e.g. 1000ml jerry can) and label (see sample below)

KEEP OUT OF REACH OF CHILDREN

Parabene Concentrate

1000ml

Batch number:_____ Date of manufacture:_____

Expiry date:_____

Pharmacy Department, Hospice Uganda, PO Box 7757, Kampala.

Expiry Date: 1 year from the date of manufacture.

Label prepared by: _____

Final product checked by: _____

WHERE THERE IS NO MORPHINE POWDER:

It is important in Africa that patients have the choice to die at home. This is the preferred place of death for the patient and carer in Africa researched in 5 countries in 2003[2627].

Thus it is important to have oral morphine.

Some countries have used injectable morphine to make up oral morphine.

Take 50 ampoules of 10mgs in 1 ml, break open and syringe out and put into jug.

Add clean drinking water to 500mls

Add green colourant

OR IF 15MGS IN 2MLS:

5mgs/5ml strength (green)

1. Morphine injection 15mg/2ml ---------- 2ml
2. Add safe drinking water to 15mls
3. Measure off 1 ml is equivalent to 1mg
4. Measure off 2.5ml is equivalent to 2.5mg.

However to make 50mgs/5ml strength (pink): cannot use 15mgs in 2mls.

To make 50mgs/5ml strength (pink):

1. Morphine injection 10mg/1ml -------- 50mls (50amps) is equivalent 10mg/8ml

26 Sepulveda C., Habiyambere V., Amandua J., et al (2003) Quality Care at End of life in Africa BMJ: 327:209-213

27 Kikule E., (2003) A good death in Uganda: survey of the needs for palliative care for terminally ill people in Urban areas BMJ ;327:192-194

2. Add safe drinking water to --------- 50ml (maybe less on withdrawal)

3. Measure off 1ml is equivalent to 10mg

Preservative not required as it is in the injection preparation.

This is presently being used successfully in Sudan.

Appendix 4: CONTINUOUS SUBCUTANEOUS INFUSION OF MORPHINE

An alternative method of obtaining analgesia or control of vomiting, when the patient is unable to effectively ingest medication, is via a continuous subcutaneous injection. As stated above, this has proved non acceptable to most patients here in Uganda and we have still managed using buccal administration and rectal administration of morphine and other medications, to keep the patient comfortable.

SC infusion obviously requires more in the way of equipment, which in turn adds cost to a palliative care service. However, under appropriate circumstances and if the equipment is available then continuous subcutaneous administration of drugs can be both useful, appropriate and very effective.

METHODS OF SUBCUTANEOUS CONTINUOUS INFUSION:

The aim is to; Deliver a given quantity of drug or drugs over a given amount of time, usually subcutaneously.

> *"We have found that we use continuous infusion of drugs in less than 0.5% of patients and not at all in the last 10 years. However in developed countries up to 75% of patients are receiving medications by this route before death". HAU 2011*

A butterfly needle is inserted appropriately under the skin over the abdomen, upper arm or thigh.

The following methods have been used:

1. Leaving a syringe attached to a subcutaneous butterfly needle in situ and instructing the relatives to push in a measured amount every 4 hours. This is only suitable if the patient is going home.

INDICATIONS:

Uncontrollable vomiting
Complete dysphagia
Occasional cases of intestinal obstruction
When per-rectal administration is Inappropriate
Severe weakness

The end stages of the disease when the patient is expected to die within 24 – 48 hours. However if the team is able to visit, this may be very comforting and affordable in a difficult situation.

2. The commonest way in UK is to use a syringe driver. This needs attention every day, which is sometimes not available from the overstretched team in the African context. Further details are below.

3. Infusion pump. These are more expensive and more complicated. However, they can deliver medication over longer periods and therefore convenient for the over committed team when the patient is at home. An example of such a pump is the CADD pump.

PROBLEMS AND SOLUTIONS:

1. Choice of delivery: Involving the patient and family:

Use of a syringe driver must be discussed with patient, family and other doctors caring for the patient as there is often a fear about

using such "machines" and some feel that this will shorten the life of the patient. This is not the case when used appropriately.

2. Which machine? This involves simplicity, convenience, availabilty and cost:

Machines can go wrong. Often the simpler the machine the less likely is there to be a problem. There are many types of infusion pump or syringe drivers available, the most tried and tested probably being the battery driven "Graesby pump". These are generally very reliable but have an initial high cost and require purchase of batteries.

Cheaper and simpler versions include the "Springfusor". As suggested this is powered by a spring and does not need batteries thus reducing the maintenance cost. It is less accurate than the Graesby pump but this is insignificant in the clinical context.

3. Drug doses can be miscalculated and when administering, all steps should be checked by, at least, two nurses.

DRUGS:

1. Drugs should be diluted, usually with sterile water, but saline can be used except for use with cyclizine when it causes crystallization.

2. Tried and tested combinations are documented in appropriate texts such as the BNF (prescribing in palliative care), The Palliative Care Formulary (Twycross et. al.)

3. Beware combinations of high doses and any combinations of three or more drugs must be used with caution. Diazepam, chlorpromazine and prochlorperazine are too irritant to be given subcutaneously Drugs should be changed every 24 hours and the site of injection checked.

CALCULATING REQUIRED DOSE:

Step 1: If the patient has already been on oral morphine, calculate the total dose given in 24 hours; e.g. 10mg four hourly = 60mg/24 hours.

Step 2: The ratio of conversion of oral to parenteral morphine is 3:1 e.g.

60mg/24 hours oral morphine = 20mg/24 hours of parenteral morphine.

Dosage requirement should be reassessed daily and incrementally increased or decreased as appropriate.

NB. Towards the end of life renal function may deteriorate and this can lead to an accumulation of morphine and other drugs. Side effects are then manifested and the dose should be reduced.

The following combinations may be used:

Morphine + Cyclizine

Morphine + Metoclopramide

Morphine + Haloperidol

Morphine + Hyoscine

Morphine + Midazolam

Appendix 5: DISPOSING OF UNUSED MORPHINE:

According to International Law, unused morphine solution should be destroyed and the destruction recorded by two people. This is possible if it is returned to the pharmacy.

However in Africa many patients live far away from the pharmacy and have many things to attend to after the death of their loved ones, and may not be able to reach the pharmacy.

Therefore we instruct the families of the patients to pour unused liquid morphine into the latrine (toilet). When the palliative care team carries out their bereavement visit they must check on this and advise the family, or check on it by phone.

The destruction of the left over morphine should be recorded in the case sheet, whether in the pharmacy or in the home, by the palliative care team.

Appendix 6: MINIMUM ESSENTIAL DRUGS REQUIRED FOR PAIN AND SYMPTOM CONTROL IN UGANDA, 2012

Generic Drug Proprietary Dose Form

Generic Drug	Proprietary	Dose	Form
Amitryptyline	Lentizol	10, 25, 50mg	tabs
Phenytoin	Epanutin	100mg	tabs/liq
Acetyl salacylicacid	Aspirin	300mg	tabs
Diclofenac	Volterol	25, 50, 75, 100mg	tabs
		75mg/3mls	inj
Codeine		30mg	inj
Morphine		5mg & 50mg/5mls	liq
chlorpromazine	Largactil	10,25mg	inj & tab
haloperidol	Serenace	5mg	tab
dexamethasone	Decadron	0.5,2mg	tab
		8mg/ml	inj
diazepam	Valium	2.5, 10mg	inj & tab
frusemide	Lasix	20,40mg	inj & tab
spironolactone	Aldactone	50,100mg	tab
ketoconazole	Nizoral	200mgs	tab

nystatin		100 & 500,000iu	Tab/susp
magnesium trisilicate			liq
metoclopramide	Placil	10mg	inj & tab
metronidazole	Flagyl	200mg	tab
amoxycillin		250mg	cap
bisocodyl	Dulcolax	5mg	tab
hyoscine butylbromide	Buscopan	10mg	inj & tab
chlorpheniramine	Piriton	4mg	tab

Nurse Jerith in Little Hospice Hoima, qualified to prescribe morphine in Uganda, instructs a patient and family in taking oral morphine in the home

SECOND LINE DRUGS AND PREPARATIONS INCLUDING THOSE FOR OPPORTUNISTIC INFECTIONS

Generic Drug Proprietary Dose Form

Generic Drug	Proprietary	Dose	Form
chloroquine		250mg	tab
		40mg/ml	inj
artemether		50mg	tab
doxycycline		100mg	
cloxacillin		250mg	tab
cotrimoxazole	septrin	480mg	tab
ciprofloxacin		500mg	tab
mebendazole		100mg	tab
clotrimazole		100mg	pess
fansidar		525mg	tab
ibuprofen		200mg	tab
indomethacin		25mg	tab
baclofen		10mg	tab
cimetidine		150mg	tab

Solutions and ointments			
chlorhexidine and cetramide		1.5/15%	
concentrate			
clotrimazole 1% cream			

hydrocortisone 1% cream			
Acyclovir/ Metronidazole/ Nystatin (Herpetic) solution			
zinc and castor oil cream			
chloramphenicol 0.5% eye drops			
Gentamycin eye drops 0.3%			
Petroleum jelly			
Glycerine suppositories			
Aqueous cream			

Note: This list may be expanded to allow for recent advances from time to time

It is essential to have these medications in constant supply to assure pain and symptom control to cancer patients.

The cheapest medications available will always be used and expensive alternatives only used for those who cannot tolerate usual medications.

Appendix 7: MAKING SUITABLE PREPARATIONS FOR PALLIATIVE CARE USE:

The patient receiving palliative care is often weak and has reduced renal clearance. This is most obvious in the weeks before death. It is therefore important that the pharmacist can make preparations suitable in strength and in acceptable formulations.

Eg if haloperidol is found to be only available as 10mgs and we need to give 1 mg daily to a patient with nausea, the tablet can be crushed and diluted in water. If the patient is vomiting then this solution can be absorbed from the buccal mucosa in strength of 1mg per ml as large volumes are not easily tolerated.

Other useful solutions that are useful in palliative care are given as per protocol at Hospice Africa Uganda 2011 below. As we move forward we will find other circumstances that require new solutions, initiated by the doctor, nurse and pharmacist. If you find successful examples of such please share with each other and us!

USEFUL FORMULAE FOR RELIEF OF LOCAL PAINS:

Herpetic solution is used to control pain and treat herpetic ulceration of the mouth or genitalia.

FORMULA FOR HERPETIC SUSPENSION

HOSPICE AFRICA, UGANDA PHARMACY DEPARTMENT

Batch number: _____ Date of manufacture: _____

Expiry date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Acyclovir 200mg tablet			2 tablets		
Metronidazole 200mg tablet			2 tablets		
Nystatin oral suspension 100,000i.u. in 1ml			30ml		

Method:

Crush the acyclovir and metronidazole tablets to a fine powder in a clean, dry mortar.

Gradually add small amounts (approximately 1 to 2ml) of the nystatin suspension to the powder to make a smooth, consistent paste.

Add the remaining nystatin suspension to the paste and mix thoroughly with the pestle to achieve a uniform suspension. Pour the suspension back into the nystatin bottle.

Re-label the product **HERPETIC SUSPENSION** (see sample label below).

Sample Label:

SHAKE THE BOTTLE BEFORE USE

Herpetic Suspension **30ml**

Apply a small amount to the affected area x 4 a day

Name: Date:

KEEP OUT OF REACH OF CHILDREN

Pharmacy Department, Hospice Uganda, PO Box 7757, Kampala.

Expiry Date: 7 days from the date of manufacture.

Storage Conditions: Store in a cool dark place.

Label prepared by: _____

Final product checked by: _____

Metronidazole mouthwash is given for smelly lesions of the mouth or smell from cancer of the oesophagus, larynx or bronchus.

FORMULA FOR METRONIDAZOLE MOUTHWASH

HOSPICE AFRICA, UGANDA PHARMACY DEPARTMENT

Batch number: _____ Date of manufacture: _____

Expiry date: _____

Ingredient	Batch No	Exp date	Qty	Measured by	Checked by
Metronidazole 5mg in 5ml infusion			50ml		
Orange squash (Quencher)	N/A	N/A	50ml		
Freshly boiled, cooled, water	N/A	N/A	To 500ml		

Method:

Measure the metronidazole infusion in a graduated cylinder and pour into a clean 500ml mineral water bottle.

Measure the orange squash in the same graduated cylinder and add it to the bottle.

Make up to final volume with water (add water to fill the bottle) and shake the bottle to mix mouthwash thoroughly.Label the product (see sample label below).

Sample Label:

SHAKE THE BOTTLE BEFORE USE

Metronidazole Mouthwash 500ml

Use 20ml to rinse the mouth twice a day.

Name: Date:

KEEP OUT OF REACH OF CHILDREN

Pharmacy Department, Hospice Uganda, PO Box 7757, Kampala.

Expiry Date: 7 days from the date of manufacture.

Storage Conditions: Store in a cool dark place.

Label prepared by: _____

Final product checked by: _____

FINALLY:

Clinicians in palliative care are the Doctor, Nurse, Clinical Officer and Pharmacist. We must all work together, within the ethos, to share the challenges of the pharmacists and dispensers in Africa.

The pharmacists have a huge ethical responsibility to bring down the price of oral morphine, so that it is available to the poorest. Governments should aim to have this available free to those in need as long as the International records are kept. This means that prescribers must have full training before using this medication which is essential to palliative care.

Then affordable oral morphine can be accessible to all in need in each country of Africa.

If morphine is not available to all in need, then holistic palliative care is impossible. Let us join hands to care for the suffering and bring peace with families and God before life closure.

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