



INSIDE STORIES

Pneumococcal
Immunization of
HIV + Patients

3

Sub-therapeutic
rifabutin levels
during treatment

6

Severe Sepsis in
resource limited
settings

10

ASK ATIC:

12

Rational management of respiratory infections: a brief summary

G Levy Hara⁽¹⁾ and E Vlieghe⁽²⁾

(1) Infectious Diseases Unit, Hospital Durand, Buenos Aires, Argentina. Co-chair, International Society of Chemotherapy Antimicrobial Stewardship Working Group.

(2) Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

Upper respiratory tract infections (URTI)

Pharyngitis:

Acute pharyngitis is considered one of the main causes of inappropriate use of antibiotics. Studies done worldwide show us that even though physicians know that about 80% of them are caused by viruses, the majority of people with sore throats and fever (50-85%) are treated with antibiotics. The reasons usually expressed by doctors are "... to calm down the patient or his/her mother..."

Streptococcus pyogenes is the main etiology of bacterial pharyngitis. Streptococcal infections should be suspected in children and teens (3 to 18 years).

Suggestive Signs and Symptoms:

- sudden onset of pain in the throat
- fever
- headache
- prominent edema of uvula
- anterior cervical lymphadenopathy
- absence of other respiratory symptoms.

On the other hand, the absence or insidious onset of fever accompanied by other signs of respiratory infection (conjunctivitis, rhinitis, cough, mouth ulcers, etc) suggest a viral etiology.

Nowadays, Centor criteria have regained value in differentiating between viral and bacterial throat infections. The Centor Criteria were developed by RM Centor et al. as a method to quickly diagnose the presence of Group A streptococcal infection in "adult patients who presented to an urban emergency room complaining of a sore throat." The patients were judged on four criteria:

- History of fever
- Tonsillar exudates
- Tender anterior cervical adenopathy
- Absence of cough

Many studies suggest that the presence of the three or four variables has a 40 - 60% positive predictive value that a culture from the throat will test positive for Group A *Streptococcus* bacteria. The absence of three or four variables has a negative predictive value of greater than 80%.

Taking into account the Centor criteria, some national bodies e.g. The National Institute for Health and Clinical Excellence (NICE) recommends that patients with three to four criteria, should be treated with antibiotics without performing microbiological studies (cultures or rapid tests)

Patients with less than three criteria should not be given antibiotics but should be managed conservatively with antipyretics and analgesics.

For those who finally need antibiotic treatment, penicillins are recommended

- IV/IM Benzyl Penicillin 2MU every 4-6 hours for 5 days benzylpenicillin,
- Oral amoxicillin 500-1000mg every 8 hours for 7-10 days.

References for articles in this Issue are available on request.

EDITORIAL

In this issue we tackle a very important topic - rational use of antibiotics in our resource-limited settings.

In 1985 at the WHO conference in Nairobi, the term *rational drug use* was defined as *"Patients receive medications appropriate to the clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community."*

Studies have shown that overprescribing, multi-drug prescribing, misuse of drugs, use of unnecessary expensive drugs and overuse of antibiotics and injections are the most common problems of irrational drug use by prescribers as well as consumers.

Irrational use of drugs wastes meager resources and results in poor patient outcomes and adverse drug reactions. It can also

stimulate inappropriate patient demand, and lead to reduced access and attendance rates due to medicine stock-outs and loss of patient confidence in the health system.

Furthermore, irrational use of antimicrobials is leading to increased antimicrobial resistance. This has contributed to the emergence and spread of resistant organisms in the community such as *Streptococcus pneumoniae*.

The significance of improving drug use would yield both financial and public health benefits. First of all, the patients would save their meager resources by not purchasing unnecessary expensive drugs. Rational use of antibiotics would also reduce the spread of resistant organisms in the community. Overall, it would increase patient confidence in the health system hence more utilisation.

Allen Mukhwana
Editor

Editorial COMMITTEE

Ceppie Merry | HIV Physician and Pharmacologist, Trinity College Dublin and Infectious Diseases Institute
Prof. Walter Schlech | Dalhousie University, Canada
Prof. Allan Ronald | University of Manitoba, Canada
Mairin Ryan | HIV Pharmacist and Pharmacoeconomist, IMB
Kim Scarsi | HIV Clinical Pharmacist, Northwestern Memorial Hospital, Chicago
Charles Steinberg | Consultant Training Department, Infectious Diseases Institute
Lydia Mpanga Sebuyira | Head of Training Department, Infectious Diseases Institute
Allen Mukhwana | ATIC - Research and Communication
Stella Zawedde-Muyanja | ATIC - Medical Officer
Barbara Namirembe | ATIC - Pharmacist

REVIEWERS

Robinah N. Lukwago | Pharmacist and Public Health Specialist
Francis Kalemeera | Senior Program Associate, Management Sciences for Health, Namibia
Mohammed Lamorde | Clinical Pharmacology Research Fellow, Infectious Diseases Institute and Research Associate, Trinity College Dublin
Monica Amuha Grace | Pharmacist, MPS

continued from page 1

Rational management of respiratory infections

Patients should be advised to take their medication for the entire duration recommended as interrupting treatment leads to early relapses in about 60% of cases.

Sinusitis:

The common cold sometimes referred to as viral rhinosinusitis is a mild disease that involves, in 90% of cases, the paranasal sinuses. After a few days, the mucous discharge frequently becomes purulent secondary to neutrophilic migration, both in viral and bacterial infections. Thus, the presence of purulent nasal discharge is absolutely not an indication for the use of antibiotics. Symptoms of the common cold often last between 6 - 9 days. In about 25% of cases, nasal congestion, rhinorrhoea, and cough may persist for up to 2 weeks. Radiological studies and antibiotic prescriptions are not recommended in the common cold.

About 2 % of common cold episodes in adults and 5-13% of these episodes in children

evolve to bacterial sinusitis. Persistence or reappearance of common cold signs beyond or after two weeks may be indicative of bacterial super-infection. These signs often are rhinorrhea (purulent or not), facial or odontogenic complaints (unilateral is more specific), sinus tenderness on palpation, low grade fever and /or unspecific malaise (headache, myalgias, arthralgias, weakness).

Radiological studies are no longer recommended because they show some degree of sinus involvement even without bacterial infection.

Once the diagnosis of bacterial sinusitis is established, we need to determine if the patient has an acute sinusitis (lasting between 10 to 30 days) or a recurrent episode (particularly in allergic people).

In, acute sinusitis, *S. pneumoniae* is the main etiology, and amoxicillin 500-1000 mg every

8 hrs for 7-10 days is the regimen of choice. Some experts suggest higher doses (1000 mg every 6 hours). A macrolide e.g. erythromycin or clarithromycin is a good alternative in allergic patients.

In recurrent episodes, in addition to *S. pneumoniae*, *H. influenzae*, *M. catharralis* and less frequently, *S. aureus* may be involved. Also, prolonged periods of nasal blockage may lead to a higher prevalence of anaerobic bacteria. Then, a rational and clever approach should be used to select the optimal antibiotic for each individual patient. For example, some patients may have a history of responding well to amoxicillin in which case, we would not need to change it but others may need amoxicillin-clavulanate-.

In these situations, doxycycline may also be useful. Finally, fluoroquinolones (e.g. ciprofloxacin) may be used.

continued on page 4

Pneumococcal Immunization of HIV Positive Patients in Africa: A Time for Revaluation?

Prof. W F Schlech



Invasive disease due to *Streptococcus pneumoniae* is a major cause of morbidity and mortality in patients with HIV infection. Common manifestations in the African context are sepsis, bacteremic lobar pneumonia, and meningitis. Indeed, recurrent bacterial pneumonia is an AIDS-defining condition in patients with HIV infection.

All aspects of the immune system are adversely affected by untreated HIV infection. This includes the inadequate production of specific responses to invading pathogens such as *S. pneumoniae*, where control of infection depends on development of opsonic antibody to the capsular polysaccharide of the organism.

Ironically, initial studies of immunization against invasive streptococcal disease (IPD) were carried out in South African gold miners in the pre-HIV era (1). These studies demonstrated that the vaccine derived from the polysaccharide capsule of *S. pneumoniae* (PPV) could prevent morbidity and mortality in this population. Further evaluation of PPV, incorporating expanded pneumococcal serotypes, have led to recommendations in developed countries to immunize all adults > 65 years in addition to younger patients with underlying chronic diseases such as diabetes mellitus and congestive heart failure that predispose them to IPD (2). More recently, the development of a protein-conjugate pneumococcal polysaccharide vaccine (PCV) with enhanced immunogenicity for use in children has

led to inclusion of this vaccine in routine childhood immunization programs in the West (3). These have reduced morbidity and mortality from IPD, as well as the incidence of otitis media, a cause of substantial childhood morbidity and an occasional harbinger of meningitis. In Uganda PCV has not yet been rolled out to all children because of cost e.g. a single dose of the vaccine costs between Ugshs 100,000 - 170,000 at private clinics. A person needs 4 doses to complete the schedule.

The role of pneumococcal immunization in HIV infected patients has been less clear. Estimates of protective efficacy using the 23-valent PPV have been between 50-70% in the pre-HAART era. The Prevention of Opportunistic Infections Working Group of the IDSA has however recommended that all patients diagnosed with HIV, including children greater than 2 years of age, should receive a single dose of the 23-valent PPV at the time of diagnosis. A recent revision in the HAART-era suggests that patients should have this immunization delayed until the CD4 cell count is above 200 or to re-immunize the patient if immediate immunization has already been given (4).

In Africa, where ironically, the initial PPV studies were carried out, pneumococcal immunization has had a "checkered" history, particularly in HIV (+) patients. In a randomized, controlled trial of Ugandan adults, the 23-valent PPV was found to be ineffective and in fact "all cause pneu-

monia" was more frequent in the vaccine arm (5). However none of the ~ 1,400 patients in the study, of whom half received the vaccine, were treated for their HIV infection. Interestingly, a follow up report 6 years following this trial confirmed an excess of "all cause pneumonia" in the vaccine recipients but found a survival advantage that favored immunization and suggested that the use of PPV in HIV infection in Africa was still open to study (6).

In children <2 years old, where PPV is ineffective, the PCV, incorporating expanded serotypes of *S. pneumoniae*, has demonstrated efficacy. A study of a 9-valent PCV in non-HIV infected children in the Gambia showed an efficacy of 77% against IPD caused by vaccine serotypes as well as a reduction in mortality (7). A subsequent trial in South Africa of almost 20,000 children was 83% effective in prevention of IPD, although this was reduced to 65% in HIV- infected children (8). Notably, there also was a reduction in antibiotic resistant *S. pneumoniae* infections, a growing worldwide problem. While cost remains an issue in resource-limited settings (RLS), use of a PCV incorporating the most common serotypes prevalent in Africa should be a part of routine childhood immunization in HIV (+) and HIV (-) children in Africa.

Despite the results of the Ugandan study of PPV in adult HIV (+) patients, the development of the more immunogenic PCV has led to new investigations of PCV in HIV (+) adults. A subset of surviving patients from the Uganda study (54 PPV and 55 placebo recipients) were given the 7-valent PCV and antibody responses to immunization occurred for all serotypes after the first dose (9). This study was followed by a randomized, controlled trial of the 7-valent PCV in Malawi. In that study, individuals who had recovered from a previous episode of IPD were given PCV or placebo and followed for subsequent pneumococcal infection. The vaccine was a highly effective (74%) in reducing subsequent IPD (10). Although there was no overall effect on mortality the study was complicated in its interpretation by the roll-out of ARVs in Malawi and more wide spread use of trimethoprim-sulfamethoxazole (Septrin®) for OI prophylaxis. With this proven evidence of the effectiveness of PCV in adult HIV (+) Africans in secondary prophylaxis, clearly the debate on pneumococcal immunization in primary prophylaxis needs to be reopened.

Summary

The effectiveness of PCV with expanded representation of serotypes of *S. pneumoniae* common in Africa suggests that a strategy of immunization against IPD may become an important intervention if issues of vaccine delivery and cost can be overcome in RLS countries. This strategy must however await the results of a large randomized, controlled trial of PCV in adult patients with HIV infection in Africa, similar to the trial in children in Soweto. Results of such a study would finally determine whether pneumococcal immunization will benefit PLWHIV in Africa.

continued from page 2

As in the other URTI, adequate symptomatic treatment (antihistamines, decongestants, analgesics etc) is pivotal.

Lower respiratory tract infections (LRTI)

Definitions:

Infections of the lower respiratory tract include mainly bronchitis and pneumonia.

Bronchitis may present as acute illness or as an acute exacerbation of chronic bronchitis. Bronchitis is often caused by viral respiratory agents and does not require antibiotic treatment. Acute exacerbations of chronic bronchitis are often due to super-infection from bacteria colonizing the nasopharynx (*S. pneumoniae*, *H. influenzae*, *K. pneumoniae*).

Pneumonia is classified according to its epidemiological context (community-acquired, hospital-acquired) or to its clinical presentation (lobar, 'interstitial' or 'bilateral').

We will focus further on Community Acquired Pneumonias as these are very common and potentially life-threatening clinical condition.

Epidemiology:

Community acquired pneumonias are an important cause of morbidity and mortality in Sub Saharan Africa especially among people living with HIV/AIDS (PLHA) and other immuno-suppressed patients e.g. the elderly, those who have had splenectomies, and those with severe co-morbidity e.g. sickle cell anaemia, chronic heart failure. In HIV Infection, community acquired pneumonias are not limited to those with very low CD4 cell counts.

The major pathogens associated with community acquired pneumonias are *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Legionella* species, *Haemophilus influenzae* and *Staphylococcus au-*

reus.

S. pneumoniae has been reported as accounting for approximately 1/3 of all cases of bacteraemic pneumonia.

'Atypical' (non-lobar) pneumonia in HIV patients may be caused by viruses (e.g. influenza virus), parasites (e.g. *P. jiroveci*), fungi (e.g. *Cryptococcus* or *Histoplasma* sp.) and above all by *M. tuberculosis*. All HIV-patients with community acquired pneumonia, especially those living in a TB-endemic area, should be investigated for TB.

Diagnosis:

The diagnosis of community acquired pneumonias combines clinical and -where available- radiographic and laboratory elements. The WHO-IMAI guidelines emphasize routinely checking for cough and acute respiratory symptoms in all patients, especially those already known with HIV. In more severe cases and where possible, chest X-ray for confirmation of the presence of infiltrates is recommended. Other recommended diagnostic tests especially in hospitalized and severely ill patients include blood and sputum cultures

Treatment

Severity assessment:

In the IMAI guidelines, WHO suggests a risk assessment based on clinical criteria (see below). Increased risk for adverse outcomes has been observed in the immuno-suppressed.

Supportive care:

As many patients with severe pneumonia present also with sepsis or septic shock, optimal supportive care, including early fluid resuscitation, administration of oxygen and close monitoring of vital parameters are as essential as adequate antibiotic therapy. These measures have been described together as 'care bundles'

Annex 1. Initial assessment of HIV patient with cough or respiratory symptoms (adapted from WHO-IMAI guidelines)

Use this classification table in all with cough or difficult breathing:

SIGNS:	CLASSIFY AS:	TREATMENTS:
One or more of the following signs: • Very fast breathing or • High fever (39°C or above) or • Pulse 120 or more or • Lethargy or • Not able to walk unaided or • Uncomfortable lying down or • Severe chest pain.	SEVERE PNEUMONIA OR VERY SEVERE DISEASE	<ul style="list-style-type: none"> Position. Give oxygen. Give first dose IM antibiotics. If wheezing present, treat (p. 80). If severe chest pain in patient 30 years or older, use Quick Check. If known heart disease and uncomfortable lying down, give furosemide. Refer urgently to hospital. Consider HIV-related illness (p. 57). If on ARV therapy, this could be a serious drug reaction. See Chronic HIV Care module.
Two of the following signs: • Fast breathing • Night sweats • Chest pain	PNEUMONIA	<ul style="list-style-type: none"> Give appropriate oral antibiotic. Exception: If second/third trimester pregnancy, HIV clinical stage 4, or low CD4 count, give first dose IM antibiotics and refer urgently to hospital. If wheezing present, treat (p. 80). If smoking, counsel to stop smoking. If on ARV therapy, this could be a serious drug reaction; consult/refer. If cough > 2 weeks or HIV-positive, send sputum for AFB. Advise when to return to the clinic immediately. Follow up in 2 days (p. 68).
<ul style="list-style-type: none"> Cough or difficult breathing for more than 2 weeks or Recurrent episodes of cough or difficult breathing which: <ul style="list-style-type: none"> Wake patient at night or in the early morning or Occur with exertion. 	POSSIBLE CHRONIC LUNG OR HEART PROBLEM	<ul style="list-style-type: none"> Send sputum for AFB (record in register). If sputum sent recently, check register for result. See follow-up TB (p. 69). If smoking, counsel to stop. If wheezing, treat (p. 80). Advise when to return to the clinic immediately.
Insufficient signs for the above classifications	NO PNEUMONIA COUGH/COLD, OR BRONCHITIS	<ul style="list-style-type: none"> Advise on symptom control. If smoking, counsel to stop. If wheezing, treat (p. 80). Advise when to return to the clinic immediately. If HIV positive, follow up in 3-5 days.

Care bundle for hospitalized community acquired pneumonias patients (adapted from Rello J, Critical Care 2008, 12 (Suppl 6): S2

Care Bundle for hospitalized Community Acquired Pneumonia patients

1. Risk assessment
2. Early fluid resuscitation
3. Prompt oxygenation
4. Immediate antibiotic therapy according to guidelines
5. Consider more intensive nursing care

Antibiotics:

Empiric treatment for community acquired pneumonias should cover mainly *S. pneumoniae* and in selected cases (e.g. chronic bronchitis, recent hospitalization) other pathogens (e.g. *H. influenzae*, *K. pneumoniae*, *S. aureus*). Unfortunately, good evidence is lacking on the bacterial spectrum causing community acquired pneumonias as well as resistance patterns in tropical limited-resource settings with high rates of HIV infections.

Penicillins e.g. amoxicillin remain first choice antibiotics for community acquired pneumonias with erythromycin or other macrolides being an alternative for patients with penicillin-allergy in countries with low level resistance of *S. pneumoniae* to this class of drugs.

Data from Southern Africa suggest high rates of co-trimoxazole and penicillin resistance among pneumococci. A recent review study on blood stream infections in sub Saharan Africa showed an overall 9.7% penicillin resistance among 628 tested *S. pneumoniae*, in contrast to 21.4% resistance for chloramphenicol, 38.6% for co-trimoxazole and 46.1% for tetracycline.

Recommendations by WHO for the treatment of mild-moderate and severe community acquired pneumonias are shown in table 1.

Table 1: Recommended antibiotic choices for community acquired pneumonias, adapted by the authors from 2009 WHO-IMAI guidelines

	mild to moderate pneumonia (oral)	severe pneumonia (IV/IM)
first choice	amoxicillin 500 mg q8 x 5d Gentamycin 5mg/kg q 24hr	ceftriaxone 2 g q24
second choice	(co-trimoxazole 160/800 mg q12 x 5d)* doxycycline	ampicillin 50 mg/kg q6 + gentamicin mg/kg q24
alternatives	erythromycin 500 mg q6 x 5d doxycycline 100 mg q12 x 5d clarithromycin 500 mg q12 for 10 days azithromycin 500 mg q24 for 7-10 days	
	*not recommended in most settings due to high resistance rates	

In view of the emerging resistance, other authors and guidelines suggest that doses of oral penicillin be increased to 1000 mg every 6 hours. The therapeutic role of co-trimoxazole in the era of resistance and frequent prophylactic use is probably very limited, whereas the use of fluoroquinolones should be strongly discouraged in view to its potential role in treatment for TB and typhoid fever, and the increasing trend towards resistance in pneumococci.

For patients with persistent symptoms of community acquired pneumonias, a differential diagnosis with other etiologies should be strongly considered, mainly TB or PJP.

The prevalence and role of the 'atypical' organisms (i.e. *Legionella*, *Mycoplasma* and *Chlamydia* spp.) in this setting is unclear; there is no recommendation for routine coverage of atypical organisms at present.

The currently recommended duration of antibiotic therapy for mild to moderate episodes of community acquired pneumonia is 5-7 days. Antibiotic therapy should be continued for 2-3 days after the patient becomes afebrile. In severe or complicated episodes, the antibiotic treatment duration may be prolonged on a case by case basis.

► What to do in HIV-positive patients with SEVERE PNEUMONIA OR VERY SEVERE DISEASE when referral is impossible

- ❖ Send sputum samples for AFB if possible.
- ❖ Treat empirically for bacterial pneumonia with IM antibiotics.
- ❖ If patient has very fast breathing or is unable to walk unaided, treat empirically for *Pneumocystis pneumonia* (PCP)
 - Give cotrimoxazole: 2 double-strength or 4 single-strength tablets three times a day for 21 days (15mg/kg of TMP component). Give supplemental oxygen if available.
- ❖ Assess the patient daily. Consult and discuss case with medical officer if possible (via phone, etc.) and continue to try to refer:
 - Check the patient with pneumonia using the Look and Listen part of the assessment:
 - Is the breathing slower?
 - Is there less fever?
 - Is the pleuritic chest pain less?
 - How long has the patient been coughing?
- ❖ After 3-5 days, if breathing rate and fever are the same or worse, start standardized, first-line TB regimen if available, or refer to district hospital. Do not start an incomplete regimen. Once TB treatment is started, treatment should be completed.
- ❖ If breathing slower or there is less fever, start first line oral antibiotic (for bacterial pneumonia) and finish 7 day course. If PCP treatment started, continue cotrimoxazole for three weeks.

Annex 2. Assessment of HIV patient with severe pneumonia (adapted from WHO-IMAI guidelines)

► Follow-up pneumonia

- ❖ After 2 days, assess the patient:
 - Check the patient with pneumonia using the Look and Listen part of the assessment on p. 16.
 - Also ask, and use the patient's record, to determine:
 - Is the breathing slower?
 - Is there less fever?
 - Is the pleuritic chest pain less?
 - How long has the patient been coughing?
- ❖ Treatment:
 - If signs of SEVERE PNEUMONIA OR VERY SEVERE DISEASE or no improvement in pleuritic chest pain, give IM antibiotics and refer urgently to hospital.
 - If breathing rate and fever are the same, change to the second-line oral antibiotics and advise to return in 2 days.
Exception: refer to hospital if the patient:
 - has a chronic disease or
 - is over 60 years of age or
 - has suspected or known HIV infection
 - If breathing slower or less fever, complete the 5 days of antibiotics. Return only if symptoms persist.
- ❖ Also:
 - If still coughing and cough present for more than 2 weeks, send 3 sputums for TB or send the patient to district hospital for sputum testing.
 - Consider HIV-related illness (p. 57).
 - If recurrent episodes of cough or difficult breathing and a chronic lung problem has not been diagnosed, refer patient to district hospital for assessment.

Annex 3. Follow-up assessment of HIV patient with pneumonia (adapted from WHO-IMAI guidelines)

Guidelines:

Within the '3 x 5' HIV-care roll-out campaign, WHO published the 'Integrated Management of Adolescent and Adult Illness' (IMAI)-modules in 2000 with revisions in 2004 and 2009. These modules contain practical and applicable guidelines for the diagnosis and acute care of HIV-related complications including community acquired pneumonias.

Sub-therapeutic rifabutin levels during treatment with lopinavir/ritonavir

Dr Mohammed Lamorde,

Clinical Pharmacology Research Fellow, Infectious Diseases Institute and Research Fellow, Trinity College Dublin.

Introduction

In Africa, HIV and tuberculosis (TB) co-infection is the leading cause of death among HIV-infected patients. When HIV-infected patients develop TB, simultaneous treatment for TB and HIV is often required. However, HIV/TB co-treatment is often complicated by pharmacokinetic drug interactions (i.e. when a drug alters the concentrations of a co-administered drug within the body). Clinically significant drug interactions commonly occur between protease inhibitors and rifamycins.

Rifamycins (rifabutin and rifampicin) are antibiotics which are critical for TB treatment success. Consequently, these drugs are an integral component of anti-TB regimens. Conversely, protease inhibitors are reserved for use in antiretroviral (ARV) regimens for HIV-infected patients experiencing treatment failure to their initial regimens. The most widely used protease inhibitor is lopinavir co-formulated with low-dose ritonavir (LPV/r). For rifamycins and ARVs, it is important to ensure that drug concentrations are maintained within the therapeutic range throughout dosing in order to prevent drug resistance.

Protease inhibitors and cytochrome P450 metabolism

Protease inhibitors are rapidly eliminated from the body by a liver enzyme called cytochrome P450 3A4 (CYP3A4). Low dose ritonavir is co-administered with LPV because ritonavir inhibits CYP3A4 activity. This interaction increases LPV concentrations in blood and ensures that adequate concentrations of LPV are available to suppress HIV replication and prevent disease progression. The effect of ritonavir on LPV is overcome by potent inducers of CYP3A4 such as rifampicin. During co-administration with rifampicin, LPV/r concentrations in blood are dramatically reduced. Therefore, co-treatment using standard doses of LPV/r and rifampicin is contraindicated.

LPV/r increases rifabutin levels in blood so a lower dose of rifabutin is recommended

Unlike rifampicin, rifabutin is a weak inducer of CYP3A4. It is the preferred rifamycin for

TB treatment in patients receiving LPV/r because it has a negligible effect on LPV/r concentrations. Rifabutin is metabolized by CYP3A4 but CYP3A4 function is inhibited by ritonavir. Consequently, when LPV/r is co-administered with rifabutin, rifabutin concentrations in blood are increased. Side effects of rifabutin (neutropenia, eye disorders and hepatotoxicity) are more likely to occur when rifabutin concentrations in blood are elevated. Therefore, it is recommended that rifabutin doses should be decreased during LPV/r co-treatment from the standard dose of 300 mg thrice weekly to an adjusted dose of 150 mg thrice weekly. The reduced dose was expected to maintain therapeutic levels of rifabutin during LPV/r co-treatment and minimize the risk of adverse events.

Recent studies show that rifabutin levels may be inadequate at 150 mg thrice weekly with LPV/r

Unfortunately, two recently published studies suggest that rifabutin levels are inadequate when administered at the adjusted dose (150 mg thrice weekly) in most patients receiving LPV/r. The first study reported of 5 cases (4 were men, 3 were Black Africans) co-treated with LPV/r plus rifabutin 150 mg thrice weekly. In all 5 cases, concentrations of rifabutin were below therapeutic levels for TB treatment. For two patients, rifabutin doses were increased to 300 mg thrice weekly but only one patient achieved therapeutic levels.

These findings were confirmed in a second well-conducted intensive pharmacokinetic study among 10 HIV/TB co-infected patients (8 were of African descent). Low rifabutin concentrations were measured in 9 out of 10 patients receiving rifabutin 150 mg thrice weekly plus LPV/r. The dose of rifabutin was therefore increased to 300 mg thrice weekly for 8 out of the 9 patients. (9th patient was excluded from study.) The findings of the second study are particularly worrying because one patient acquired rifampicin resistance during rifabutin treatment.

It is not well understood why patients had lower than expected rifabutin concentrations during LPV/r treatment. However, the guidance to adjust doses of rifabutin down to 150 mg thrice weekly was based on data from a small study in healthy volunteers. It is possible that the differences seen may be a disease effect (i.e. an effect of HIV and/



or TB on rifabutin pharmacokinetics). This postulation is supported by data from the second study which showed that 5 out of 10 patients already had low rifabutin levels at 300 mg thrice weekly before they commenced ARVs. It is therefore possible that HIV/TB co-infected patients may have higher rifabutin requirements than healthy volunteers.

These two studies suggest that many LPV/r-treated patients receiving the recommended adjusted rifabutin doses may have low rifabutin levels in blood. Furthermore, these low levels may put patients at increased risk of TB drug resistance.

Routine monitoring of rifabutin levels is useful, but it is impractical in most ARV clinics in Africa. Instead, studies are needed to investigate pharmacokinetics and safety of alternative doses of rifabutin in order to identify the dose that will result in therapeutic concentrations for most patients. In the meantime, until additional pharmacokinetic and safety data are available, clinicians should monitor their patients closely to assess response to TB treatment.

These studies must be viewed within the context of limited access to rifabutin in Africa. Rifabutin is not yet widely available because of its relatively high cost. However, initiatives to make rifabutin more widely available and at lower prices are underway. For example, some ARV centers in Uganda already have rifabutin for patient care and it is expected that even more centers will have access to rifabutin in the near future. Therefore, a window of opportunity exists to optimize rifabutin doses for patients receiving protease inhibitors.

CEFTRIAZONE

Monica Amuha Grace
BPharm . MPS

Ceftriaxone is a widely used broad spectrum antibiotic. It is used in the management of several conditions caused by either gram negative or gram positive bacteria.

A look at the drug profile of Ceftriaxone will help in the rational prescribing of this drug in our resource limited setting.

Mechanism of Action

Ceftriaxone is a third generation cephalosporin with a bactericidal action, inhibiting bacterial cell wall synthesis of susceptible organisms.

GRAM NEGATIVE BACTERIA	GRAM POSITIVE BACTERIA
Escherichia coli	Staphylococcus aureus (not MRSA)
Klebsiella spp	Streptococcus pneumoniae
Salmonella and shigella spp	Streptococcus pyogenes
Haemophilus influenza	Clostridium perfringens
Neisseria gonorrhoeae	
Haemophilus ducreyi	
Bacteroides fragilis	

It has greater activity than first or second- generation cephalosporins against gram- negative bacteria. However, it is less active than cefuroxime against gram-positive bacteria, most notably Staphylococcus aureus. The following organisms are susceptible to ceftriaxone;

Available formulations

500mg, 1g, 2g vial with powder for reconstitution for IV or IM injection

Indications

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftriaxone and other antibacterial drugs, ceftriaxone should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Culture and susceptibility information should be obtained where possible. This information should then be considered when selecting or modifying antibacterial therapy.

In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empirical selection of therapy.

Special Considerations

Renal and Hepatic Impairment

In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided liver function is intact. Only in cases of pre-terminal renal failure (Creatinine clearance < 10ml per minute) should the daily dosage be limited to 2g or less.

In patients with liver damage there is no need for the dosage to be reduced provided renal function is intact.

Pregnancy and Lactation

Ceftriaxone crosses the placental barrier. Reproductive studies in animals have shown no evidence of any adverse effects on the fetus. Since safety in human pregnancy is not established ceftriaxone should not be used unless absolutely indicated. Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftriaxone is administered to a breastfeeding woman.

Contraindications and Special Precautions

- Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin, or any penicillin. As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken.
- Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions or products, even via different infusion lines because of the risk of precipitation of ceftriaxone-calcium which can lead to gall stones or kidney stones. Calcium-containing products must not be administered within 48 hrs of the last administration of ceftriaxone
- Cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be used in hyperbilirubinaemic neonates (especially prematures) because they are at risk of developing bilirubin encephalopathy.

continued from page 7

Dosing : The dosage depends on the condition being treated.

CONDITION	DOSE
CNS Infection	
Brain abscess	I.V. ceftriaxone 2g every 12 hours with I.V. metronidazole and Penicillin G. for at least 6-8 weeks
Meningitis	2g b.d for 7-14 days. (longer courses may be necessary for selected organisms)
CVS Infections	
Endocarditis (management)	2-4g daily treat for 4 weeks (6 weeks for prosthetic valve endocarditis) + low dose gentamicin (stopped after 2 weeks)
Endocarditis (prophylaxis)	1g 30-60 minutes before surgical procedure
Blood Stream Infections	
Septicemia	1-2g daily in adults and 50-75mg/kg daily in Pediatrics for 7-10 days
Respiratory tract Infections	
Pneumonia	I.V 1g once daily, usually in combination with a macrolide for at least 10 days
Genitourinary Infections	
Pelvic Inflammatory disease:	250mg I.M. in a single dose plus doxycycline 100 mg PO BID for 14 days with metronidazole 400mg PO t.d.s for 14days
Syphilis	I.M. or I.V.: 1g once daily for 8-10 days
Chancroid	I.M. 250mg as a single dose
Acute epididymo-orchitis	250mg IM plus doxycycline 100mg PO 2 times daily for 10 days
Gonococcal infections (uncomplicated)	250 mg IM as a single dose
GIT Infections	
Typhoid fever	2g once daily for 14 days
Skin and soft tissue infections	
Cellulitis	1g IV once daily for 10-14 days
Surgical prophylaxis	A single dose of 1 gram administered intravenously 30 minutes to 2 hours before surgery is recommended

- Ceftriaxone may result in the overgrowth of non-susceptible organisms, such as enterococci and Candida spp. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to administration of antibacterial agents.
- Each gram of Ceftriaxone contains approximately 3.6mmol sodium. This should be taken into consideration by patients on a controlled sodium diet such as hypertensive patients.

Drug Interactions

- Ceftriaxone has potential to increase the effects of anticoagulants. Monitoring of anticoagulant effect is required.
- Efficacy of oral hormonal contraceptives may be affected by inhibiting the bacterial flora responsible for recycling ethinylestradiol from the large bowel. Supplementary (non-

hormonal) contraceptive measures should be used during treatment and for seven days following treatment

- Ceftriaxone has the potential to cause a disulfiram-like reaction with alcohol
- There are no known clinically significant drug interaction between ceftriaxone and antiretroviral therapy.

Adverse Drug reactions

The most frequently reported adverse events are diarrhea, nausea and vomiting. Other reported adverse events include; headache, dizziness, hypersensitivity reactions such as allergic skin reactions including rashes, pruritus, urticaria, dermatitis, and anaphylactic reactions (e.g. bronchospasm)

Super infections of the genital tract with yeasts, fungi or other resistant organisms.

Blood disorders including neutropenia, leucopenia, eosinophilia, thrombocytopenia, aplastic and haemolytic anaemia, Agranulocytosis (<500/m3), mostly after 10 days of treatment and following total doses of 20g ceftriaxone and more.

Increase in serum liver enzymes (AST, ALT, alkaline phosphatase), jaundice.

Pseudomembranous colitis (mostly caused by Clostridium difficile), pancreatitis (possibly caused by obstruction of bile ducts).

There may be pain at the injection site following intramuscular and intravenous infusion. Lidocaine minimizes pain due to Intramuscular injection but should NEVER be used with intravenous administration. Thrombophlebitis may occur with intravenous infusion.

Directions for Use

Intramuscular Administration: Reconstitute Ceftriaxone powder with the appropriate diluent. After reconstitution, each 1 ml of solution contains approximately 250 mg or 500mg equivalent of ceftriaxone depending on the amount of diluent.

As with all intramuscular preparations, Ceftriaxone should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Intravenous Administration: After reconstitution with an appropriate IV diluent, ceftriaxone should be administered intravenously by infusion over a period of 30 minutes.

After reconstitution, each 1 ml of solution contains approximately 100 mg equivalent of ceftriaxone.

After reconstitution, this solution can be further diluted with 0.9% Normal Saline or 5% Dextrose to make concentrations of 10mg/ml or 40mg/ml as desired.

Solutions that can be used for reconstitution include;

- sterile water for Injection,
- Normal saline,
- 5% Dextrose, and

1% Lidocaine solution (without epinephrine). Lidocaine solution is used in the reconstitution of ceftriaxone for **intramuscular administration only**.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution because they can result in particulate formation.

Storage :

Ceftriaxone sterile powder should be stored at room temperature 25°C (room temperature) or below and protected from light. After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone intramuscular solutions (250mg/ml) when reconstituted with either sterile water for injection, normal saline, 1% lidocaine or 5% dextrose remain stable (loss of potency less than 10%) for 24 hours at room temperature (25°C) and 3 days when refrigerated (4°C).

Ceftriaxone intravenous solutions, at concentrations of 10, 20 and 40 mg/mL, remain stable (loss of potency less than 10%) for 2 days at room temperature and 10 days when refrigerated (4°C) stored in glass or PVC containers :

NOTE:

After the indicated stability time periods, unused portions of solutions should be discarded.

Parenteral drug products should be inspected visually for particulate matter before administration.

Route of Administration	Vial Dosage Size	Amount of Diluent to be added
Intramuscular administration 250 mg/ml	500 mg	1.8ml
	1 gm	3.6ml
Intravenous Administration 100mg/ml	500 mg	4.8ml
	1 gm	9.6ml

Severe Sepsis in resource limited settings - Challenges and opportunities

David B. Meya

Lecturer, Department of Medicine and Infectious Disease Institute, School of Medicine, College of Health Sciences, Makerere University and Adjunct Assistant Professor; Division of Infectious Diseases & International Medicine, Dept. of Medicine, University of Minnesota, Minneapolis, MN

Introduction

Sepsis contributes to the high burden of infectious disease morbidity and mortality in both low and high income countries (HICs).

In high income countries, sepsis has been implicated as the leading cause of non-cardiac death amongst critically ill patients. (1-2).

In low income countries which suffer from a high burden of infectious diseases with a limited range of affordable antibiotics available for treating these infections, conducting studies to identify the etiology of sepsis and the appropriate anti microbial therapy should be high on the research agenda.

This article summarizes findings from the first prospective evaluation of the management and outcomes of patients with severe sepsis in a resource-constrained setting conducted in Mulago Hospital (a 1500-bed national referral hospital in Kampala, Uganda) and Masaka Regional Referral Hospital (a 330-bed regional referral hospital in Masaka, Uganda (125 kilometers southwest of Kampala). The authors conclude that with respect to degree of fluid resuscitation and appropriateness of empiric antibacterials, the management of septic patients in resource limited settings remains sub-optimal with overall mortality of 43% (3).

Challenges of severe sepsis management in High income vs Low income settings

Whereas sepsis management in high income countries consists of algorithmic approaches focusing on early diagnosis , antimicrobial treatment, aggressive fluid resuscitation and

concomitant monitoring of such parameters as central venous pressure, central venous oxygen saturation, and hematocrit to decrease sepsis-associated mortality (4), data regarding the best management practices to optimize outcomes of severe sepsis in resource limited settings remains limited.

Factors thought to contribute to poor outcomes of critically ill patients in these settings include limited antibiotic choices due to cost, deficiency of diagnostic laboratories, microbiologic and radiologic capabilities and delayed presentation of severely sick patients (5-6). A study of bacteremic children in Tanzania highlights the importance of using appropriate antimicrobial therapy with results showing increased mortality when empiric antibiotics were discordant with antibiotic susceptibility profiles (7).

Summary of The Ugandan Prospective Study

The Ugandan prospective study conducted in two hospitals had as its main objectives

- identifying clinical predictors for in-patient and post-discharge mortality among hospitalized patients with severe sepsis, and
- description of the epidemiology, management, and etiology of sepsis in this setting with particular attention to potentially cost-effective interventions such as initial fluid resuscitation and empiric antibiotic administration.

Data on appropriate empiric antibiotic therapy was collected and defined as use of a regimen to which the isolate was found to be sensitive in susceptibility testing.

Results

The majority of patients enrolled were ARV-naïve, HIV-positive women. The most frequent chief complaints at time of admission were fever, cough, and diarrhea.

Of the 380 patients followed in this study, ninety (23.7%) died while hospitalized. Median length of hospital stay

for the remaining 290 patients who survived to discharge was 6 days (IQR, 3–10). Of these patients, 43 (14.8%) were lost to follow-up.

Of the 145 total deaths, 15 (10.3%) occurred in the first day, 42 (30%) occurred within 3 days after admission, 70 (48.3%) occurred within 7 days after admission, and 105 (72.4%) occurred within 28 days after admission.

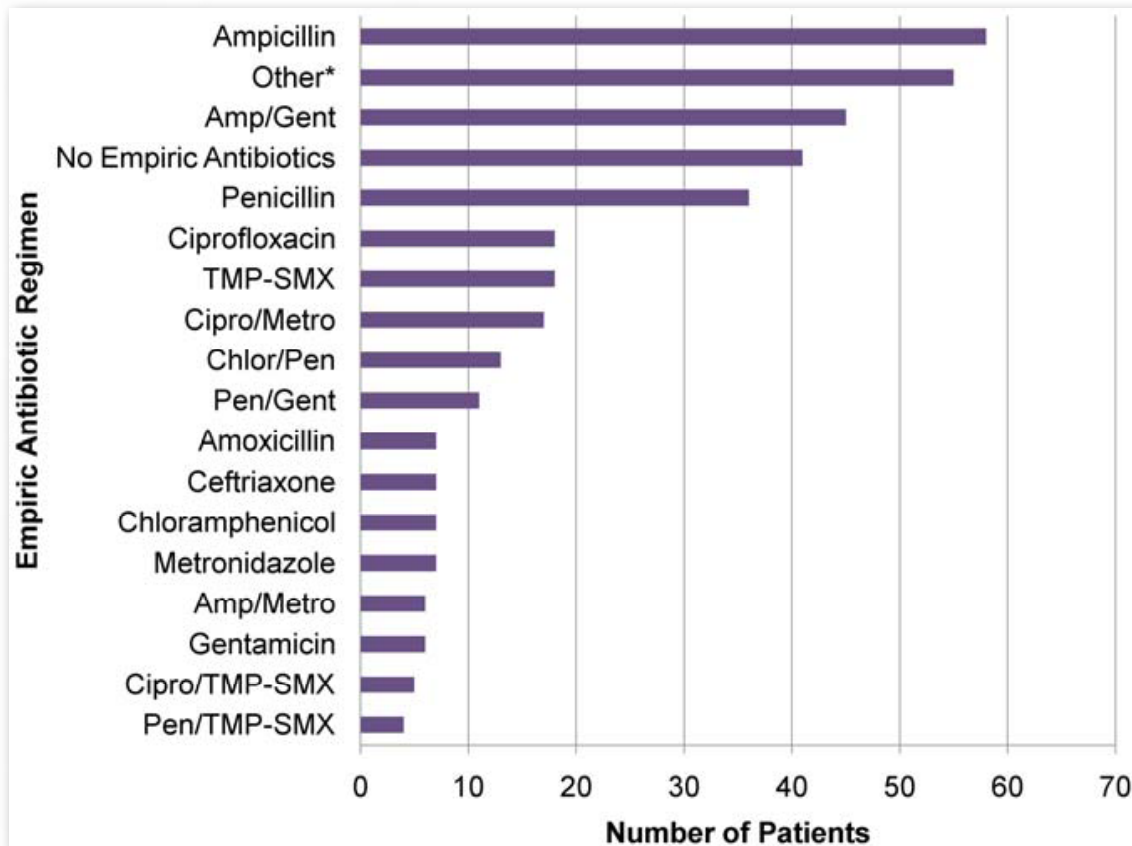
The median volume of intravenous crystalloid fluid received within the first 6 hours was 500mls (IQR 250- 1000), thus clearly no survival benefit was observed across strata of fluid volume in the general study population.

Empiric Antibacterial Administration

During the course of the study, availability of antibacterial therapy at any given time was inconsistent., 52 different empiric antibacterial combinations were used by the admitting doctors caring for the study patients (see Figure below). In total, 84.8% (319/376) of patients received some form of empiric antibacterials. There was no overall mortality benefit found between patients receiving any of the 52 available empiric antibacterial regimens compared to patients receiving no empiric antibacterials.

With respect to antibiotic susceptibilities, approximately 95% of *Salmonella* isolates were resistant to chloramphenicol and trimethoprim-sulfamethoxazole (TMP-SMX); none of the *Staphylococcus aureus* samples were resistant to oxacillin. In a subset of patients with positive aerobic cultures where susceptibilities were tested, there was a trend towards decreased overall mortality in patients receiving appropriate versus inappropriate empiric antibacterials. The most commonly isolated organisms were; *Salmonella* (20%), *Staphylococcus aureus* (12%) and *Streptococcus pneumoniae* (6%). The most appropriate antibiotic in this setting was ceftriaxone.

Frequency of separate empiric antibiotic regimens used.



[*Represents 35 separate regimens used, 1% of the time;

Pen/Gent = Penicillin/Gentamicin; Pen/TMP-SMX = Penicillin/Trimethoprim-Sulfamethoxazole; Amp/Metro = Ampicillin/Metronidazole, Amp/Gent = Ampicillin/Gentamicin; Chlor/Pen = Chloramphenicol/Penicillin; Cipro/TMP-SMX = Ciprofloxacin/Trimethoprim-Sulfamethoxazole; Cipro/Metro = Ciprofloxacin/Metronidazole; TMP-SMX = Trimethoprim-Sulfamethoxazole]

Discussion

The authors note that for patients presenting with severe sepsis, the observed mortality was lower than expected in this population possibly due to the younger population having more robust cardiovascular systems compared to much older patients with severe sepsis who are observed to have high mortality in developed settings.

Clinical predictors of in-hospital mortality in this study included

- Morbidity assessment scales (i.e., Karnofsky Performance Scale and Glasgow Comma Scale and vital signs).
- Leukocytosis and
- thrombocytopenia

Leukocytosis and thrombocytopenia were previously shown to be good outcome predictors in patients with septic shock in HIC settings but were found to be predictive of in-hospital mortality in our setting.

Until material and human resources are improved, mortality and morbidity due to severe sepsis in low income countries will

continue to remain a problem. The nurse: patient ratio of less than 1:20, insufficient intravenous fluids and poor continuous monitoring need to be addressed. Antibacterial management further needs to be better optimized in our settings. Empiric antibacterial therapy was rarely concordant with blood culture sensitivities in this study. The trends shown are consistent with several studies that have observed increased mortality in bacteremic patients receiving inappropriate empiric antibacterials (8).

Conclusion

In the current era of HAART scale-up in Sub-Saharan Africa, improvement in sepsis management may create a window of opportunity for later access to life-saving HIV therapy. Thus, focusing on being able to clinically identify this syndrome and administer appropriate management should be paramount during the training and education of all health workers who manage patients similar to those in this study. Having limited resources should not be an excuse to practice clinical medicine to the detriment of the patient.

- Severely ill patients should receive at least 20-30 mls/kg /hr of normal saline when undergoing resuscitation in the emergency setting in the first 6 hours
- If a bacterial infection is suspected, clearly chloramphenicol and trimethoprim-sulfamethoxazole are two drugs that are not useful.
- Oxacillin will be effective against Staphylococcal infections while more organisms will be susceptible to Ceftriaxone.

Some strategies that will create an environment where severely ill patients are not admitted to hospitals to die but to improve and survive are;

- procurement of sufficient Intravenous fluids,
- the use of appropriate antibiotics,
- improvement in laboratory capabilities,
- increase in health personnel which will facilitate closer monitoring of patients.



ASK ATIC:

By Stella Zawedde-Muyanja, MB ChB

Question:

We have an HIV positive patient who has been on SEPTRIN® prophylaxis for the last 2 years. She is not on ARVs and not on any other concurrent long term medications.

She has no presenting complaints this morning and has come in for monthly refill of septrin.

The CBC results from her previous visit show a CD4cell count of 300 cells/ mm³ and a neutrophil count of <500 cells / mm³ which is flagged as LOW. The rest of the blood picture is normal

How should we manage this patient now?

ANSWER:

This patient has severe neutropenia .This is an adverse drug reaction that is sometimes seen in people who take SEPTRIN®

Neutropenia is a hematological disorder characterized by an abnormally low number of neutrophils in the blood. Neutrophils usually make up 50-70% of circulating white blood cells and serve as the primary defense against infections by destroying bacteria in the blood.

The normal absolute number of neutrophils (ANC) is about 1500 cells / mm³

The severity of neutropenia is categorized as mild when the ANC is 1000-1500 cells per mm³ ,moderate when the ANC is 500-1000 cells per mm³ , severe when the ANC is less than 500 cells per mm³.

The clinician managing this patient should:

- Immediately withdraw the offending drug
- Check for signs of any other blood disorders e.g. anaemia and/or thrombocytopenia. If these are present, the patient could have a pancytopenia and will need more investigation e.g.

bone marrow biopsy .

- The patient should be examined for signs of infection :
 - The patient should be asked for a history of a fever.
 - The skin, oral mucosa, perineal and perirectal areas should be examined for rashes, ulcers or abscesses.
 - Lymph nodes should be examined as lymphadenopathy is a possible indication of a disseminated infection or possibly, malignancy.
 - The lungs should be examined for signs of pneumonia,
- If no fever is present, the patient should be offered supportive management with special attention to oral hygiene to prevent infections of the teeth or gums and good care for wounds or abrasions to prevent skin infections
- If fever is present, then the patient could have a superimposed bacterial or fungal infection. The risk of superimposed infection increases with decreasing ANC and is highest in severe neutropenia.
 - All neutropenic patients with fever, should have the following laboratory investigations done on them where possible: two sets of blood cultures, urinalysis and urine culture, sputum gram stain and culture, CXR should also be obtained to rule out pneumonia
 - Bacterial infections in neutropenic patients are usually caused by gram negative rods (E.coli, Klebsiella and Pseudomonas spp.), OR gram positive organisms especially Staph epidermidis, Staph Aureus and Streptococcal Spp.
 - Fungal infections are usually caused by Candida spp and aspergilla spp.

Treatment

Febrile episodes in neutropenic patients should be treated aggressively with systemic broad spectrum antibiotics or antifungals.

For treatment of bacterial infections the recommended drugs are:

- Combination of a third generation cephalosporin and an aminoglycoside e.g. cefixime (1.5g every 8 hrly), ceftriaxone (1-2 g daily) for 1-2 weeks plus amikacin 7.5mg/kg 12 hrly OR Gentamycin 5mg/kg for 5-7 days.
- Quinolones e.g. Ciprofloxacin 500mg B.D for 1-2 weeks, Ofloxacin 200mg B.D and Norfloxacin 400mg B.D for 1-2 weeks.
- Penicillins active against beta lactamase producing bacteria e.g. Co-amoxiclav(at 500mg of amoxicillin B.D) for 1-2 weeks can be used if combined with an aminoglycoside

For treatment of fungal infections, Fluconazole 400mg O.D for up to 2 weeks.

Prevention of Infection in patients with Neutropenia

Sometimes, oral prophylaxis is given to neutropenic patients to prevent bacterial or fungal superinfection. However, this is reserved for high risk patients with very severe neutropenia ANC <100 cells/ mm³. Prophylaxis in these patients has been seen to lead to a reduction in the number of febrile episodes.

In HIV negative patients, Quinolones e.g. ciprofloxacin, norfloxacin and ofloxacin and antifungals e.g. Fluconazole have been used with considerable success.

However, in HIV positive patients, the use of Quinolones for prophylaxis is not encouraged due to risk of development of resistance to fluoroquinolones should the patient have undiagnosed TB

Other Causes of Neutropenia:

Clinicians should look out for neutropenia in patients who are on other drugs that can cause neutropenia. These include

- anticancer chemotherapy e.g. methotrexate, cyclophosphamide,
- anti-TB drugs e.g. rifampicin, isoniazid, streptomycin ,
- anticonvulsants e.g. carbamazepine, phenytoin
- certain antibiotics e.g. cotrimoxazole, chloramphenicol , macrolides e.g. erythromycin
- ARVs mainly Zidovudine

Neutropenia can also occur in patients who have other diseases that can lead to myelosuppression e.g. cancers like leukemia, AIDS, and tuberculosis.