Antibiotic stewardship:

Factors influencing the choice and outcomes of antimicrobial therapy in a resource-limited, rural, public hospital in uMkhanyakude District, KwaZulu-Natal, South Africa: pre-intervention phase

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Abstract

Background: Resistance to antimicrobial agents has been growing rapidly and is currently a matter of concern world-wide. Irrational use of antibiotics has been highlighted as a major cause of resistance, among others.

Aims: To establish whether antibiotic prescribing at the hospital is done according to principles of rational antibiotic prescribing and to establish factors that influence the choice and outcomes of antimicrobial therapy at Mseleni hospital.

Objective: To perform an audit of all antibiotic prescriptions written at the hospital for a period of two months.

Method: A data collection tool was developed and made available to all prescribers whose permission had been obtained. The tool was used to obtain information necessary to dispense antibiotics. This information was analysed to establish the extent to which prescribers at this hospital apply the principles of antibiotic prescribing, based on the National Standard Treatment Guidelines and Essential Medicines List (STGs and EML).

Results: A hundred data collection tools (representing 100 prescriptions) meeting the inclusion criteria were selected for analysis.. Antibiotic therapy was indicated in 98% (98; n=100) of all prescriptions. In total, 16 antibiotics were prescribed 124 times. In approximately 97% (120; n=124) of cases, the prescribed antibiotic correctly matched the most likely cause of the infection. Infections were confirmed for five patients. Antibiotics were prescribed according to the National STGs and EML in 41% (19; n=46) of prescriptions. Doses were prescribed as recommended by these guidelines in 88% (88; n=100) of prescriptions. Intravenous (IV) antibiotics were prescribed for 43% (26; n=60) of inpatients. Of these, 65% (17; n=26) were later switched to oral antibiotics. Hang times were one hour or less in 25% (6; n=24) of patients receiving IV antibiotics, and between 2–56 hours in the remainder.

Conclusions: National Treatment Guidelines and medicine availability influenced choice of antibiotics. Lack of microbiological cultures led to empiric prescribing. Communication between prescribers, nurses and pharmacists influenced outcomes.

Recommendations include: Administering first doses of IV antibiotics immediately after prescription; switching IV therapy to appropriate oral therapy when patients' conditions allow; pharmacists routinely monitoring antibiotic use; utilising microbiological tests to identify patients who need antibiotics; and providing resistance patterns.

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Introduction

Resistance to antimicrobial agents has been growing rapidly and is currently a matter of concern world-wide.[1] In 2014, the World Health Organization (WHO) published a global report on surveillance, in which resistance of common infection-causing microorganisms to commonly used antibiotics was reported to be 79% on average, globally.[2] Irrational use of antimicrobial agents has been highlighted to have grossly contributed to the development of resistance, among many other causes.[1] It has been proposed that in order to combat resistance, individual institutions need to implement antibiotic stewardship programmes.[1]

Background

Causes of antimicrobial resistance

Resistance arises as a consequence of mutations in microbes and selection pressure from antibiotic use that provides a competitive advantage for mutated strains.[1] Mechanisms of bacterial resistance to different antimicrobial drugs and classes have been well studied and are available.[2,3,4] Methods for preventing resistance have also been put forward.[3] The Lancet Infectious Diseases Commission states that the causes of antibiotic resistance are complex and include human behaviour at many levels of society.[1]

A few reasons have been proposed to explain the sustained rise of bacterial resistance against antimicrobial agents world-wide. The Lancet Infectious Diseases Commission observes that the continued high rates of antibiotic use in hospitals, the community, and agriculture have contributed to selection pressure that has sustained resistant strains.[1] Inappropriate choice and sub-optimal

doses of antibiotics have also been implicated in the stepwise selection of resistance.[1,5]

Misuse of antibiotics has also been implicated as the main cause of antimicrobial resistance. The European Centre for Disease Prevention and Control has highlighted three main types of misuse: (1) inappropriate use by patients, not taking full doses as prescribed and not observing the duration of treatment, both of which lead to some bacteria surviving and becoming selectively resistant; (2) use of broad-spectrum antibiotics instead of narrow-spectrum antibiotics; and (3) the unnecessary prescription of antibiotics for conditions against which antibiotics have no effect, e.g. viral infections.

The unnecessary antibiotic prescribing is caused by a number of factors. Literature has shown that in China, for example, hospitals which rely on pharmaceutical sales for income have a tendency to overprescribe.[6] In India, it has been reported that prescribers receive compensation from drug sellers in exchange for directing patients to their pharmacies.[1] Although there is no literature showing such practice in South Africa, the "prescription-only product" requirement for antibiotics appears not to be complied with. Patients often come to retail pharmacies asking for antibiotics and when asked to present prescriptions, they respond saying "...but I usually buy it at my local chemist without a prescription".

In other African low-income and middle-income countries where health delivery systems are inadequate, prescription-only regulation might impede access to antibiotics due to shortage of trained prescribers.[1] Poverty sits at the centre of the problem, being the cause of the lack of adequate sanitation, clean water and proper hygiene. This puts people at an increased risk of acquiring infections. Moreover, individuals living in poverty also have poor baseline nutritional status and weakened immune systems, not sufficient to fight off infections.[1] These patients are also at risk of treatment termination due to affordability issues. Patients often buy the quantity of medicine they can afford, rather than the quantity required for the full course of treatment.

Consequences of antibiotic resistance

Among others, the most serious consequences of antibiotic resistance include: (1) longer duration of illness and higher rates of mortality in patients with resistant infections; (2) increase in costs of treatment for resistant infections; and (3) inability to do procedures that rely on effective antibiotics to prevent infection such as surgery, transplantation and chemotherapy.[1] Studies have shown that, without effective antibiotics, 30–40% of patients having total hip replacements would have a postoperative infection, with a case-fatality rate of roughly 30%.[7] Raised costs of antibiotic therapy are also an expected outcome of antibiotic resistance. Patients with resistant infections require far more expensive newer generation antibiotics, therefore raising out-of-pocket expenses for those who can afford, while putting a lot of pressure on the already-limited public health budget.

Principles of rational antibiotic prescribing

Rational use of antibiotics involves:

1. Deciding if an antibiotic is needed. There should be strong evidence of a bacterial infection shown either from the patient's clinical presentation (fever, raised white cell count, raised inflammatory markers e.g. c-Reactive protein), specific organ damage, or any site of infection (e.g. skin and soft tissue infections are commonly caused by gram positive cocci bacteria, urinary tract infections by gram negative bacilli, intra-abdominal infections by gram-negative, gram-positive and anaerobic organisms, etc.).[8] This information can then be used to start empiric therapy.[8]
2. Performing a microbiological culture to confirm the suspected infection and identify the infection-causing microorganism in hospitalised patients or outpatients with recurrent infections. Once the culture result becomes available, any empiric treatment should be escalated or de-escalated. Diagnostic methods promote the use of narrow spectrum antibiotics; improve patient outcomes and reduce the overall use of antibiotics, which reduces antibiotic pressure and slows induction and spread of resistance.[9,10,11]
3. Choosing the correct antibiotic with the narrowest possible spectrum of action to target the pathogens most likely to cause the infection. This is guided by[8]:
   i. Culture and resistance patterns as shown by the sensitivity tests
   ii. Contra-indications: allergies (e.g. penicillin allergy) and organ function (e.g. aminoglycosides in patients with impaired renal and vestibular functions)
   iii. Tissue penetration of the antibiotic
4. Ensuring the correct dose, frequency, duration of treatment and appropriate route of administration. Severe infections and infections of certain sites e.g. cerebrospinal fluid, blood, endocardium, bones and joints all require intravenous antibiotics.[7]
5. Initiating the antibiotic treatment as soon as possible. In severe infections, empiric therapy should be started within one hour after the antibiotic has been prescribed. Limitimg the hang time to a maximum of one hour helps to improve outcomes of treatment. Delaying administration of antibiotics leads to increased mortality. In septic shock, for example, mortality increases by 7.6% for every hour the antibiotic administration is delayed.[12]
6. Patient monitoring. The appropriateness of the prescribed antibiotic should be evaluated every 24 hours. IV therapy should be switched to oral therapy when the patient's clinical condition allows.[13]

Selecting the most appropriate antibiotic: drug-bug match

Antimicrobial agents are specific in their activity against bacteria. They may be bactericidal or bacteriostatic. They achieve their

antimicrobial activity through several mechanisms. These include: (1) inhibition of cell wall synthesis, (2) inhibition of protein synthesis, (3) inhibition of nucleic acid synthesis and (4) disruption of cytoplasmic membranes, among others. Selection of an antibiotic whose antimicrobial activity targets the specific bacteria implicated in the patient's condition is crucial to successful treatment of the infection. The selection of the antibiotic for empiric therapy should be based on the patient's clinical presentation, site of infection and specific organ damage. These give the prescriber an indication of what microorganism could be the most likely cause of the infection.[8]

For all inpatients and outpatients with recurrent infections, empiric therapy should be followed with microbiological analysis, for identification and sensitivity analysis to confirm the empiric therapy or initiate alternative therapy. Use of local antibiograms with pathogen-specific susceptibility data has been shown to be crucial in guiding the selection of the most appropriate antibiotic treatment.[14] Furthermore, rapid point-of-care diagnostic tests providing information on the pathogens and their susceptibility to antibiotic tests have been shown to have great potential to minimise inappropriate antibiotic use and improve patients' outcomes.[1]

However, in a resource-limited setting, it may not be possible to have a laboratory report. In most cases, prescribers use clinical examination based on the presenting signs and symptoms to diagnose and initiate antibiotic treatment. The clinical reasoning behind this empirical treatment is that the microorganisms causing the infection are unknown to the prescriber at the time of presentation. Hence, the prescribers opt to treat empirically in order to cover all possible causes. Use of microbiological tests would help to identify the pathogens and therefore use of narrow-spectrum antibiotics. In most cases, however, the severity of the patient's condition dictates prompt initiation of empirical treatment without culture results. Where possible, the specimen should ideally be collected before the commencement of empiric treatment.[15] Continued use of antimicrobial agents whose activity does not match the pathogen promotes resistance due to selection pressure.[1] In cases where two or more antibiotics are prescribed in empirical therapy, use of diagnostic information such as pathogen-specific susceptibility data would reduce the overall use of antibiotics.[16]

Change of treatment from one antibiotic to another

The decision to change treatment is guided by two main factors: (1) the patient's clinical condition and (2) culture results. Change of treatment is necessary when a patient starts treatment but clinically deteriorates or responds but slowly. Changing treatment could be escalation or de-escalation. Escalation involves increase in dose of the antibiotic agent or addition of another antibiotic agent to the empirical treatment. De-escalation involves a decrease in dose of the antibiotic agent, omission of an antibiotic agent from the list of empirical treatment agents or changing of treatment altogether to other treatment options as suggested by the antibiogram. Empiric combination therapy should not be administered for more than 3–5 days.[17] Once the causative organism has been identified, treatment should be de-escalated to the most appropriate monotherapy. There is no evidence showing that combination therapy is superior to monotherapy.[17]

When a patient starts a definitive treatment regimen and improves, they should continue and complete the course of treatment. If the treatment was empiric and the pathogen is not identified, the empiric therapy should be completed with appropriate IV to oral switch with an equivalent antibiotic. If the pathogen is identified by culture and a sensitivity report is obtained, the treatment should be de-escalated to the narrowest spectrum antibiotic followed with appropriate IV to oral switch.[8]

If therapy is started but with slow response or clinical deterioration, a culture should be obtained with sensitivity profile of the organism. If the culture results confirm that the antibiotic is appropriate and that the organism is sensitive to the antibiotic, the poor clinical response can be explained by one or more of the following reasons as summarised in Figure 1[8]:

i. Inappropriate medicine delivery to the site of action from the formulation caused by poor absorption or low bioavailability. This requires another appropriate formulation e.g. intravenous.
ii. Insufficient dose. Severe infections require high loading doses whereas infections in less vascularised tissues e.g. bones generally require high doses.
iii. Presence of co-morbid conditions. Concurrent initiation of Highly Active Anti-Retroviral Treatment (HAART) and Tuberculosis (TB) treatment can cause deterioration of the patient's condition due to Immune Reconstitution Syndrome (IRIS) resulting from reactivation of the immune system by the HAART.
iv. Inappropriate expectations. Some conditions like TB generally take long to respond to therapy

Aims and objectives

This study provided a baseline to the implementation of an antimicrobial stewardship programme at Mseleni hospital. The aims of the study were: (1) to establish whether antibiotic prescribing at Mseleni hospital is done according to the above principles of rational antimicrobial prescribing, and (2) to establish the factors that influence the choice and outcomes of antimicrobial therapy at Mseleni hospital. The objective of this study was to perform an audit of all antibiotic prescriptions that were written at Mseleni hospital for both inpatients and outpatients covering a period of two months.

Methodology

Ethical considerations and study design

The study comprised a prescription audit approach. Permission to conduct the study was obtained from the Provincial and District Infection Prevention and Control (IPC) committees, the medical management team and all prescribers at the hospital.

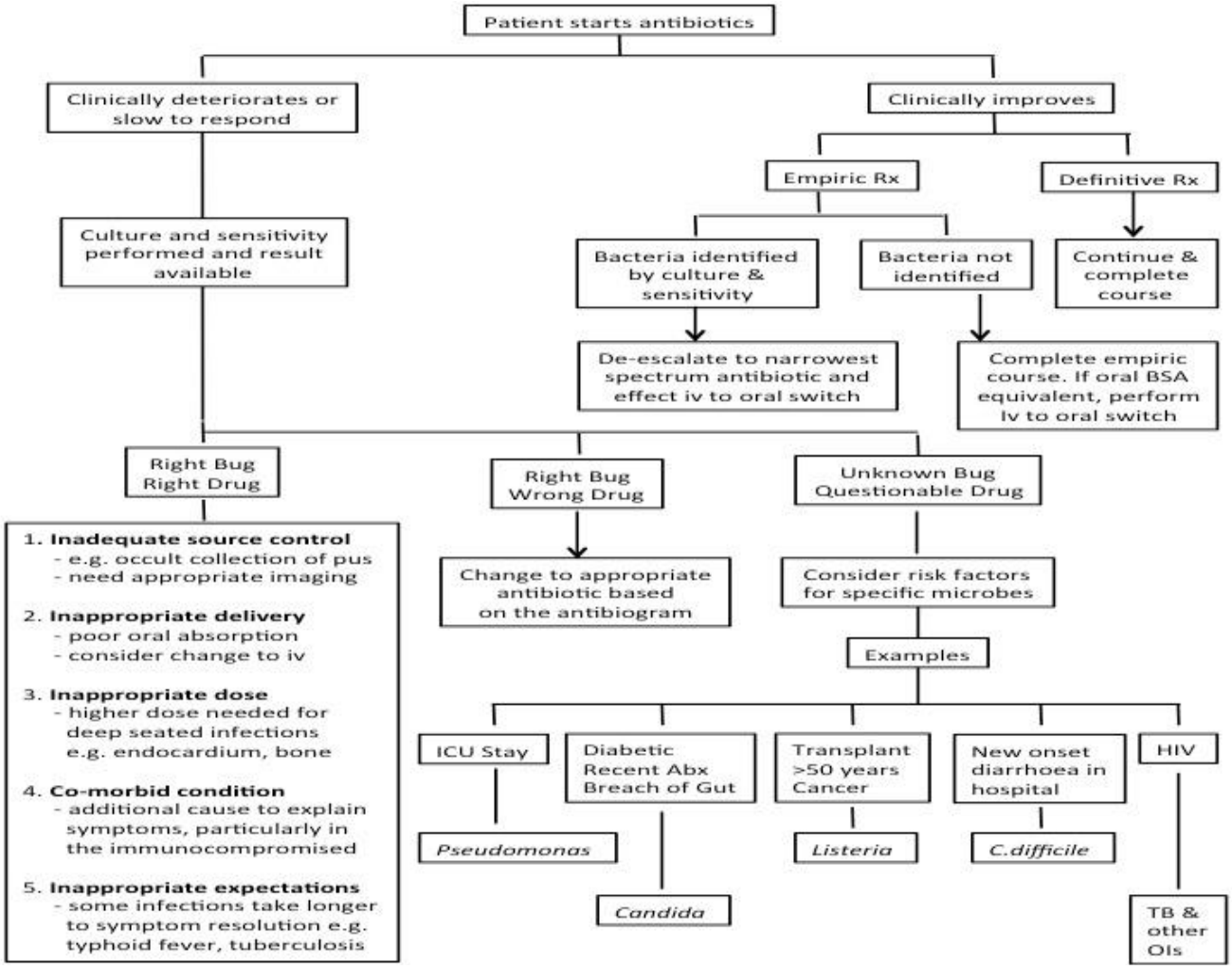

Figure 1: Algorithm for changing treatment from one antibiotic to another

Source.[8] Wasserman S, Boyles T, MendelsonM. (2014). A pocket guide to antibiotic prescribing for adults in South Africa, 2014 Published on behalf of the South African Antibiotic Stewardship Programme (SAASP)

Patient-identifying details such as name and identification number were not captured; hence, patients' consent was not obtained. The researcher held separate meetings with prescribers, pharmacy staff and the nursing staff in all wards, to notify them about the audit and their role in the data collection process.

Data collection

A data collection tool in the form of a generic prescription was developed and made available to all prescribers in the wards and in the doctors' consultation rooms at the outpatient department (OPD) at the hospital. Prescribers had been notified and requested to fill the prescription at the time they prescribed an antibiotic, alongside the usual patient medication charts/files and attach it to the patient's file. The information that was collected on the generic prescription included: (1) gender; (2) age and weight; (3) reason for admission; (4) diagnosis for which the antibiotic was prescribed; (5) method(s) used to confirm the diagnosis; (6) sensitivity of the microorganism to certain antibiotics; (7) antibiotic prescribed (name, dose, frequency and duration of treatment); (8) date and time the antibiotic was prescribed; (9) proposed date to stop the antibiotic; (10) date and time the first dose was administered (to obtain hang time); and (11) the outcome after initiation of treatment. The outcome after initiation of treatment was expected to be one of the following: (1) infection cured, (2) requires extension of duration of treatment, or (3) requires change of treatment from one antibiotic or formulation to another. The possible reasons that would necessitate such a change were expected to be one or a combination of two or more of the following: (1) patient's treatment was reviewed on a grand ward round or the patient was not responding to initial treatment; (2) a specialist was consulted and suggested such a change; (3) microbiology analysis report suggested that the treatment be escalated or de-escalated or changed; or (4) the patient's condition could allow change from intravenous formulation to an oral formulation of the same or different but appropriate (same spectrum) antibiotic. For inpatients, a section was provided for date and time to be recorded every time the antibiotic was administered by the nursing staff. This tool was then retained at

the pharmacy when the patients' medication charts/files were brought to the pharmacy for dispensing after the patient had been discharged to go home by the doctor. No contact was made with patients, for the purpose of gathering the above information. Nurses and doctors were neither interviewed nor observed. Two hundred copies of the tool were distributed and of these, 138 were collected. Only 100 of the collected copies met the inclusion criteria.

Inclusion/exclusion criteria

A prescription was considered for analysis if the accompanying tool was duly completed by the prescriber with all the necessary information required to dispense an antibiotic such as: patient's age, weight, diagnosis for which the antibiotic was prescribed, the generic name of the prescribed antibiotic, the dose, frequency, route of administration, start date and time of treatment, proposed date to stop treatment and total duration of treatment, or if the missing information on the tool could be obtained from the file by the pharmacist at the time of dispensing. Other relevant information such as reason for admission/visit, other presenting conditions and known allergies was also obtained.

Data analysis

The information on the data collection tool was used as a representation of how the patients' conditions were managed. This information was then analysed to establish whether antibiotic prescribing and administration at this hospital followed the *"Principles of Rational Antibiotic Prescribing"* described in Section 2.3. Relevant sources were consulted to establish the possible pathogens that would most likely cause infections with signs and symptoms leading to particular diagnoses such as those written by the prescriber on the data collection tool. Guidelines to antibiotic prescribing,[8] National Treatment Guidelines[18,19] and the South African Medicines Formulary (SAMF)[20] were then consulted to find the appropriate antibiotics, their doses, frequency, and duration of treatment for each of the prescribed antibiotics. Other current medical diagnosis and treatment sources[15] were also consulted, although priority was given to local sources to account for local resistance profiles. The data were then tabulated manually and summarised using simple statistical inferences such as mean, frequency and percentage. This analysis elucidated key aspects of antibiotic usage which are the focus of rational antibiotic prescribing: (1) drug-bug match; (2) escalation/de-escalation of treatment; (3) hang time; (4) dose, frequency and duration of treatment; (5) IV to oral switch where necessary. The prescriptions were also evaluated on whether or not the prescribed antibiotic was supposed to be used as such according to the National Standard Treatment Guidelines and Essential Medicines List.

Results

Mseleni Hospital is a district level hospital located in the remote areas of northern KwaZulu-Natal. This hospital serves a catchment area of two municipalities with a population of just over 100 000 people. There are 184 beds in different sections across eight wards: step down ward (8 beds), paediatrics ward (22 beds), male ward (medical 8 beds, surgical 8 beds, TB 8 beds and isolation 7 beds), female ward (isolation 7 beds, TB 8 beds, medical 8 beds, surgical 17 beds and high care unit 4 beds) and maternity ward (ante-natal care [ANC] 16 beds, kangaroo mother care [KMC] 4 beds, post-natal 16 beds, post-Caesarean 8 beds, high care ANC 4 beds, nursery 5 beds and isolation 2 beds), plus another ward where women await delivery, with 24 beds.

A hundred completed data collection tools (representing 100 patients) were selected for analysis after they met the inclusion criteria; 60 from inpatients and 40 from outpatients departments (OPD). Various infections were diagnosed in the different wards as shown in Table I. Note that these are not individual cases but a summary of all cases from all wards. Twenty-two different infections were diagnosed across all wards and OPD.

Among the prescriptions which were selected for analysis, sixteen antibiotics were prescribed 124 times for these infections. Amoxicillin/Clavulanic acid (Co-Amoxiclav) (both oral and IV formulations) was the most prescribed antibiotic followed by Amoxicillin, Ampicillin, Ciprofloxacin and IV/IM Ceftriaxone. Chloramphenicol, Phenoxymethylpenicillin (Penicillin V), Benzylpenicillin (Penicillin G) Co-Trimoxazole and Praziquantel were prescribed less frequently than other antibiotics, as shown in Table II.

Application of principles of rational antibiotic prescribing: Each time an antibiotic was prescribed, it was analysed individually based on the principles of rational antibiotic prescribing. Figure 2 summarises the extent to which the principles of rational antibiotic (in term of the STEs and EML) prescribing were observed.

Selection of appropriate empirical therapy

All diagnoses were analysed to establish if they required treatment with antibiotics. Ninety-eight per cent (98; n=100) were found to be eligible for treatment with antibiotics. The prescribed antibiotics were also evaluated to establish whether they were correctly matched with the most likely causes of the diagnosed infections, based on each antibiotic's spectrum of action; for example, a penicillin (a cell wall synthesis inhibitor) being empirically prescribed for an infection that is most likely caused by a gram positive streptococcus infection and not a gram negative streptococcus infection, against which it is not effective.[7,15,18,19,20] Approximately 97% (120; n=124) of the time an antibiotic was prescribed, it was found to be correctly matched with the most likely cause of the infection.

Use of microbiology and other tests to confirm presence of infections

Only five diagnoses were confirmed: one LRTI by a chest X-Ray, three UTIs by urine dipstick tests and one recurrent abscess by a microbiological analysis, with a sensitivity report. All other cases were treated empirically.

Choosing the appropriate antibiotic

Reference was made to the National Standard Treatment Guidelines and Essential Medicines List, hospital level for both adults (2012 edition)[18] and paediatrics (2013 edition).[19] Out of 100

Table I: Summary of infections diagnosed and the antibiotics prescribed for their management

Ward	Infection/diagnosis	Antibiotic regimen prescribed	Regimen recommended by STGs and EML
OPD	Lower Respiratory Tract Infection (LRTI)	Co-Amoxiclav, PO q8h x $^{5}/_{7}$	[18]Diagnosis not available in Standard Treatment Guidelines and Essential Medicines List (STGs and EML)
	Upper Respiratory Tract Infection (URTI)	Amoxicillin PO q8h x $^{5}/_{7}$	[18]Diagnosis not available in STGs and EML
	Male Urethral Syndrome (MUS)	Ciprofloxacin PO q12h x $^{5}/_{7}$	[21]Cefixime PO stat + Doxycycline q12h x $^{7}/_{7}$
	Urinary Tract	Co-Amoxiclav PO q8h x $^{5}/_{7}$	[18]Co-Amoxiclav PO q8h x $^{5}/_{7}$ (If pregnant)
	Infection (UTI)	Ciprofloxacin PO q12h x $^{3}/_{7}$	[18]Ciprofloxacin PO. Uncomplicated cystistis: single dose. Complicated cystistis: q12h x $^{7}/_{7}$
	Bilharzia (UTI during pregnancy)	Praziquantel stat	[20]Praziquantel stat
	Conjunctivitis (not specified on script)	Chloramphenicol eye ointment q12h x $^{5}/_{7}$	[18]Chloramphenicol or Gentamicin ophthalmic drops q4–6h (day). Chloramphenicol ointment (night)
	Otitis media	Amoxicillin PO q8h x $^{5}/_{7}$	[21]Amoxicillin PO q8h x $^{5}/_{7}$ [18]Ciprofloxacin PO q12h x $^{5}/_{7}$
	Dog bite wound	Co-Amoxiclav PO q8h x $^{7}/_{7}$	[18]Diagnosis not available in STGs and EML
	Abscess	Flucloxacillin PO q6h x $^{5}/_{7}$	[18]Often "incision and drainage" sufficient. If indicated, Flucloxacillin PO q6h x $^{5}/_{7}$
		Cephalexin PO q8h x $^{7}/_{7}$	Flucloxacillin (and 2nd line [Clindamycin]) not available in pharmacy stock at the time of prescription and dispensing
	Recurrent abscess	Azithromycin PO q24h x $^{3}/_{7}$	Sensitivity profile available: S: Cloxacillin, Erythomycin, Azithromycin and Clindamycin. R: Ampicillin, Co-Amoxiclav
	Knee injury	Flucloxacillin PO q6h x $^{5}/_{7}$	[18]Diagnosis not available in STGs and EML
	Vaginal Discharge (VD)	Ceftriaxone 250 mg IM stat + Azithromycin 1 g PO stat + Metronidazole 2 g PO stat	[18]Diagnosis not available in STGs and EML
	Vaginal Discharge Syndrome (VDS)	Azithromycin 500 mg PO q24h x $^{3}/_{7}$ + Metronidazole 400 mg PO q8h x $^{7}/_{7}$	[21]Cefixime PO stat + Doxycycline q12h x $^{7}/_{7}$ (Amoxicillin PO q8h x $^{7}/_{7}$ if pregnant) + Metronidazole 2 g stat)
	UTI/VDS	Ceftriaxone 250 mg IM stat + Azithromycin 1 g PO stat + Metronidazole 2 g PO stat + Cefalexin 500 mg PO q8h x $^{5}/_{7}$	[18]Diagnosis not available in STGs and EML
	Cellulitis	Co-Amoxiclav PO q8h x $^{5}/_{7}$	[18]Cloxacillin IV q6h, switch to PO q6h (not available in stock)
	Acute tonsillitis (not specified if viral/bacterial)	Phenoxymethylpenicillin (Pen V) PO q12h x $^{10}/_{7}$	[21]Benzathine penicillin 1.2MU IM Single dose or Pen V q12h x $^{10}/_{7}$, (Erythromycin q6h x $^{10}/_{7}$ if penicillin-allergic)
Maternity ward	LRTI	Co-Amoxiclav IV q8h x $^{7}/_{7}$	[18]Diagnosis not available in STGs and EML
	Systemic sepsis, meningitis?	Ceftriaxone IV q12h x 10/7	[18]Treatment depends on the source/cause of infection
	Pyelonephritis	Co-Amoxiclav IV q8h x 2/7 + Co-Amoxiclav PO q8h x 5/7	Gentamycin (or Ceftriaxone: impaired renal function) IV q24h changed to Ciprofloxacin PO q12h for a total of 7 days
	VDS	Metronidazole PO q12h x $^{7}/_{7}$	[21]As shown above
	UTI (urine dipstick: leukocytes present)	Cefalexin PO q8h x 5/7 + Co-Amoxiclav PO q8h x 5/7 + Ciprofloxacin PO q12h x 3/7	[18]Ciprofloxacin PO. Uncomplicated cystistis: Single dose. Complicated cystistis: q12h x 7/7
	Neonatal sepsis	Ampicillin IV q8h x 5/7	[22]Cefotaxime IV q8h x 10/7 + Gentamicin q24h x 7-10/7
HCU	Infective endocarditis?	Cloxacillin IV q6h x 28/7 + Gentamycin IV q24h + Penicillin G IV q6h x 28/7	[18]Penicillin G IV q6h x 28/7 + Gentamycin IV q24h + Cloxacillin IV q6h x 28/7
	UTI (admitted for post surgery wound sepsis)	Ciprofloxacin 500 mg stat	[18]Ciprofloxacin PO. Uncomplicated cystistis: Single dose. Complicated cystistis: q12h x $^{7}/_{7}$
	VDS	Ceftriaxone 250 mg IM stat + Azithromycin 1 g PO stat + Metronidazole 2 g PO stat	[21]Cefixime PO stat + Doxycycline q12h x $^{7}/_{7}$ (Amoxicillin PO q8h x $^{7}/_{7}$ if pregnant) + Metronidazole 2 g stat)
Female Ward	UTI (confirmed with urine dipstick: leucocytes present)	Cefalexin PO q8h x 15/7	[18]Ciprofloxacin PO. Uncomplicated cystistis: Single dose. Complicated cystistis: q12h x 7/7
	PCP (community-acquired)	Ceftriaxone IV q24h x 5/7	Penicillin G (or Ampicillin) IV q6h. Switch to Amoxicillin PO q8h. Add Erythromycin PO q6h if poor response after 48–72 hrs. Total duration; at least 5 days
		Co-Trimoxazole PO q8h x 7/7	

Ward	Infection/diagnosis	Antibiotic regimen prescribed	Regimen recommended by STGs and EML
Female Ward	Bronchitis	Amoxicillin PO q8h x 5/7	Amoxicillin PO q8h x 5/7 (only for severe exacerbations of chronic bronchitis)
	Pneumonia	Co-Amoxiclav IV q8h x 2/7 + Co-Amoxiclav PO q8h x 5/7	Co-Trimoxazole PO q6h x 21/7. Some patients were kept on IV therapy for 7 days
	Sepsis	Co-Amoxiclav IV q8h x 7/7	[18]Treatment depends on the source/cause of infection
	Septic arthritis, abscess and cellulitis	Co-Amoxiclav IV q8h x 2/7 + Co-Amoxiclav PO q8h x 5/7	Cloxacillin IV q6h x 28/7. May change to oral therapy after 2 weeks of IV therapy in patients with good clinical response.
	Dysentery	Ciprofloxacin PO q12h x 7/7	Ciprofloxacin PO q12h x 3-7/7
	Post-surgical wound sepsis	Flucloxacillin PO q6h x 7/7	Cloxacillin IV q6h followed by Flucloxacillin PO q6h to complete 5–10 days of therapy. Vancomycin IV q12h if Cloxacillin/MRSA
Male ward	Pyelonephritis	Ceftriaxone IV/IM q24h x 7/7	Gentamycin q24h (or Ceftriaxone q24h if impaired renal function) switched to Ciprofloxacin PO q12h to complete 7 days
	Septicaemia	Ceftriaxone IV q12h x 3/7	[18]Treatment depends on the source/cause of infection
	Abscess on right foot	Cloxacillin IV q6h x 5/7	[18]Often "incision and drainage" sufficient. If indicated, Flucloxacillin PO q6h x 5/7
	Wound sepsis	Co-Amoxiclav PO q8h x 7/7	Cloxacillin IV q6h followed by Flucloxacillin PO q6h to complete 5–10 days of therapy. Vancomycin IV q12h if Cloxacillin/MRSA
	UTI with kidney stones	Ciprofloxacin PO q12h x 3/7	[18]Ciprofloxacin PO. Uncomplicated cystistis: Single dose. Complicated cystistis: q12h x 7/7
Paediatrics ward	LRTI	Amoxicillin PO q8h x 7/7 Ampicillin IV q8h x 7/7 Gentamicin q24h x 7/7	[19]Diagnosis not available in STGs and EML
	Secondary skin infection	Cloxacillin IV q8h x 7/7 Co-Amoxiclav PO q8h x 7/7	[19]Diagnosis not available in STGs and EML
	Severe asthma exacerbation	Amoxicillin PO q8h x 3/7	[19]Diagnosis not available in STGs and EML
	Osteomyelitis	Cloxacillin IV q6h x 7/7	[19]Cloxacillin IV (or Vancomycin IV q6h if MRSA) + Cefotaxime IV (or Ceftazidime IV q6h + Gentamycin IV q24h) (infants) or Ceftriaxone IV (children)
	Acute gastroenteritis	Ampicillin IV q6h x 7/7	[19]Antibiotic not necessary unless dysentery or Severe Acute Malnutrition (SAM) present
	Pneumonia (not specified)	Ampicillin IV q6h x 2/7 + Amoxicillin PO q6h x 5/7	[19]Treatment depends on whether the condition is due to anaerobic, mycoplasma or chlamydia, staphylococcus, opportunistic (secondary to HIV infection), or nosocomial infection. However, none of the treatments matched with recommended treatments for any of the above infections
		Gentamicin IV q24h x 7/7	
		Ceftriaxone IV/IM q24h x 5-7/7	
		Co-Amoxiclav IV q8h x 2/7 + Co-Amoxiclav PO q8h x 5/7	
Key	x/7: Number of days, PO: Orally, q: every, h: hours, stat: immediate once-off dose, S: Sensitive, R: Resistant, MRSA: Methicillin-resistant *Staphylococcus aureus*		

Table II: Most frequently prescribed antibiotics

Antibiotic	Prescription frequency	Percentage	Antibiotic	Prescription frequency	Percentage
Co-Amoxiclav	34	27.42	Cephalexin	5	4.03
Amoxicillin	18	14.52	Cloxacillin	5	4.03
Ampicillin	13	10.48	Flucloxacillin	4	3.23
Ciprofloxacin	11	8.87	Penicillin V	1	0.81
Ceftriaxone	11	8.87	Penicillin G	1	0.81
Azithromycin	6	4.84	Co-Trimoxazole	1	0.81
Gentamycin	6	4.84	Chloramphenicol	1	0.81
Metronidazole	6	4.84	Praziquantel	1	0.81

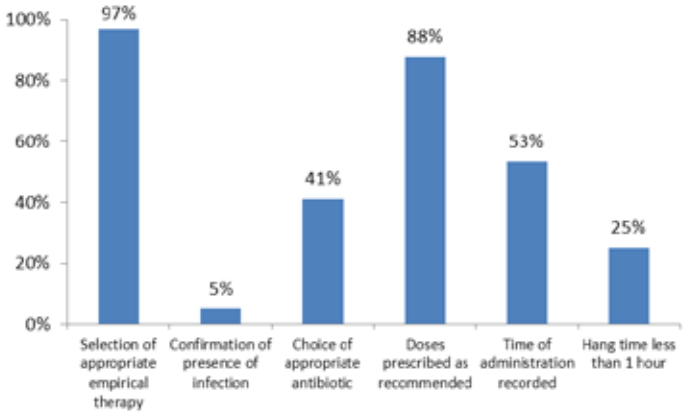

Figure 2: Extent to which principles of rational antibiotic prescribing were observed

prescriptions which met the inclusion criteria, 46 were selected for analysis under this section (others were repetitions of these). Antibiotics were prescribed for the respective diagnoses as recommended by these guidelines in only 41% (19; n=46). The others were not prescribed according to these guidelines either because some conditions (such as URTI or LRTI) were not available in the STGs and EML as diagnosed (21%: 10; n=46), or because the antibiotic of choice was not available in the hospital pharmacy's stock (8%: 4; n=46) (the pharmacy staff make available to the prescribers a list of low/no stock medicines on a weekly basis). The source of 28% (13; n=46) of the prescribed regimens could not be established.

Ensuring appropriate dose, frequency and duration of treatment

Doses were prescribed as recommended by the STGs and EML in 88% (88; n=100) of all prescriptions, less than recommended in 7% of the prescriptions and higher than recommended in 5% of the prescriptions. The frequency ranged from stat doses, once daily doses, twice daily, three times, up to four times daily. The durations of treatments ranged from one to 10 days. The average duration of all treatments was seven days.

Timely administration of treatment; the hang time

Hang time is the period of time taken to administer the first dose of an IV antibiotic after it has been prescribed. In severe infections, IV antibiotics should be administered as soon as they are prescribed. The hang time should be kept below one hour for better outcomes.[12] Time for administering the first dose of the medicines was recorded in 53% (32; n=60) of the inpatients, although only 24 of these received IV antibiotics. The hang time was up to one hour in 25% (6; n=24) of these. All the rest, 75% (18; n=24), had a hang time ranging from 2–56 hours; with an average of 12.7 hours, a median of 10 hours, lower and upper quartile averages of 3.7 and 31.0 hours respectively.

Intravenous (IV) to oral switch

Switching from IV to oral formulation of the same antibiotic is a practice that is used to minimise usage of intravenous medications, thereby saving costs. It is based on several inclusion and exclusion criteria.[13] In total, intravenous antibiotics were prescribed for 43% (26; n=60) of the inpatients. Of these, 65% (17; n=26) were later switched to oral formulations with three at lower than recommended doses, 10 with recommended doses and four at doses higher than those recommended by the National STGs and EML. The rest, 34% (9; n=26), were maintained on IV antibiotics throughout the durations of treatment. The post-intervention phase of this project will encourage IV to oral switch as soon as it is possible to do so and also monitor cost-saving benefits of this practice.

Discussion of some of the factors affecting the choice and outcomes

Use of microbiological analysis to confirm diagnoses

Microbiological analysis is currently underutilised as both a diagnostic tool and a method to curb antibiotic resistance yet the reliability and cost effectiveness thereof can both not be underestimated. In the USA, it has been shown that diagnostics only account for 2% of health expenditures, yet guide 60–70% of treatment decisions.[17] In this district, the situation is rather different; the microbiology laboratory services have in fact, expressed a concern that this service is currently being underutilised. This complaint has been reflected in the results of this study, in which one culture was requested in a period of two months. Several factors affect this resource from being leveraged.

In this District, only two hospitals have laboratory facilities which can do microbiological cultures. Access to this service is not limited but also not practical owing to the distance to these facilities and the nature of the analysis itself. This analysis takes time and the turn-around time is high; indicating microbiological growth in a sample in at best 24–48 hours. Typically, getting a microbiological laboratory report with a sensitivity profile takes 5–7 working days from the date of receipt of the sample. Given that the majority of the patient conditions presenting at the outpatient department (OPD) responded to short courses of 3–7 days of empiric antibiotic treatment, using microbiology laboratory reports for recurrent infections for outpatients remains the most viable option.

The average duration of treatment for inpatients of seven days also showed that empirical therapies were successful in treating infections without microbiology culture results, rendering culture results not directly beneficial for specific patients from whom samples were taken. Nevertheless, the practice of sending samples and obtaining microbiology results is beneficial for providing area-specific antibiotic resistance patterns, which is obviously beneficial towards empirical therapies prescribed for patients on subsequent admissions.

The hang time

A few reasons may have contributed to the long delays before initial doses of IV antibiotics were administered. When the patient is admitted, the ward nurses wait for the usual times at which they give medicines to all patients. The time of giving medicines is not

personalised to each patient. The administration of medicines in the wards is fixed at 5–7am, 2–4 pm and 8–10pm. The nurses also take a long time to collect medicine from the pharmacy, citing that they are busy in the ward but the majority claim they were not on duty on the day the medicine was prescribed. This affected patients who were admitted from 7am to 4pm on Mondays to Thursdays and it explains the lower quartile hang times of 2–6 hours.

Lack of communication between doctors, nurses and pharmacists and medicine shortages contributed to very long hang times. It was noticed that when the prescribed medicine was not available, the pharmacist indicated that the medicine was out of stock but only on the prescription. The pharmacist did not inform the prescriber with a possible alternative which could be prescribed. The nurse would then take the prescription back to the ward and also not inform the prescriber of the shortage for another antibiotic to be prescribed. When this happened towards the end of the day, the prescriber would only know about the patient not receiving the prescribed medicine the next time they were doing a ward round, usually in the morning of the following day. This mainly affected patients who were admitted from 4pm to 10pm on Mondays to Thursdays and it explains the median hang times of 7–13 hours. This also affected those who were admitted from Fridays to Sundays which explains the upper quartile hang times of 23–56 hours.

Conclusions

Compared to other factors, the National Treatment Guidelines and Essential Medicines Lists were found to have a higher influence on the choice of antibiotic treatment prescribed. However, the compliance rate was low (41%). This compliance was in certain circumstances affected by the lack of stock of the antibiotic recommended by the guidelines (8%) or by some of the conditions not being stated in the guidelines as diagnosed (21%). Neither the source nor the rationale for prescribing some of the treatments (28%) could be established.

A literature review showed that microbiological analysis has a direct influence on antibiotic prescribing although it is not commonly used or not used at all. When used, culture and sensitivity results help prescribers to select antibiotics to which the pathogens are sensitive, therefore avoiding resistance and ensuring a high treatment success rate. Hence, use of diagnostic tests has a direct influence, not only on the choice of antibiotic prescribed, but also on treatment outcomes. However, timely access to results from the available microbiology laboratories is far from being practical at this hospital and hence, patients presenting with particular signs and symptoms of infections are treated for all possible causes.

Communication between the prescribers, the nurses and the pharmacists had an indirect influence on the treatment outcomes. Poor communication negatively influenced the hang times. Lack of microbiological analyses, medicine stock-outs and poor communication between prescribers, nurses and dispensers make it impossible for the prescribers to follow the principles of rational antibiotic prescribing.

Recommendations

Use of diagnostic tests

Rapid point-of-care diagnostic tests providing information on the pathogens and their susceptibility to antibiotic tests are required in order to identify patients who need antibiotics. This strategy would have great potential to minimise inappropriate antibiotic use. Rapid diagnostic tests for detection of causative agents or biomarkers at the time the patients present themselves to the hospital would allow timely and specific targeting with narrow-spectrum antibiotics. This would in turn shorten the time patients stay in the wards and improve outcomes.

Much as the turn-around time of the culture results is high and may not be in time for the particular patient for whom it was requested, microbiological analysis has a crucial public health benefit: antimicrobial resistance surveillance. The sensitivity profiles of the microorganisms may act as a source of resistance patterns that can be used to shape local infection control programmes and to change both regional and national treatment guidelines.

This surveillance, however, is a structural strategy against antibiotic resistance (among others: restrictive and persuasive) and it requires technology which is still expensive, infrastructure to run it and maintain it, and trained personnel to operate it under supervision. These are not yet available at this hospital, but given the individual patient and public health benefits that this strategy generates, it's a goal worth aiming for. The infrastructure and technology should be phased in as resources become available or as new facilities are built.

Communication

Communication between prescribers, pharmacists and nurses needs to be a habit. Currently, pharmacists communicate with prescribers through the nurses but evidence has shown that the message is not transmitted. Pharmacists also communicate counselling information on how to use the medicines through the nurses because nurses collect inpatients' medication from the pharmacy, especially when the patients are being discharged from the hospital. It is not known whether this crucial information on how to use the dispensed medicines reaches the intended recipient. It is necessary that a pharmacist routinely visits the wards to ascertain patients' understanding on how to take their medicines.

Hang time and IV to oral switch for IV antibiotics

In order to achieve desired hang time of one hour, it was recommended that the first dose of IV antibiotics be given immediately at OPD when the patient is diagnosed and admitted. Patients requiring IV antibiotics need to be evaluated on a daily basis in order to establish if the patients' conditions have improved so the therapy can be switched to oral antibiotics. This will in turn reduce IV antibiotic use.

Emphasis on clinical antibiotic use and outcomes

It is necessary to have a (clinical) pharmacist who would be dedicated to overall therapeutic drug monitoring but putting special attention on the following aspects of antibiotic use especially for inpatients: (1) choice, dose, frequency and duration of treatment of any antibiotics prescribed; (2) infection-related mortality; (3) length of stay in the wards; (4) re-admission rates; (5) encourage and monitor sample collection and use of culture results; and (6) trends of antibiotic use.

Further reviews

Regular reviews of this nature need to be carried out routinely at all hospitals not only in this district but throughout South Africa, to monitor and promote rational antibiotic use.

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Conflict of interest

There is no conflict of interest to declare.

References

1. Laxminarayan R, Duse A,Wattal C, et al. (2013). Antibiotic resistance - the need for global solutions. The Lancet Infectious Diseases Commission. http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0ahUKEwjk3ZTT97jJAhWG2RoKHQqgC8oQFggrMAI&url=http%3A%2F%2Fwww.reactgroup.org%2Fuploads%2Fnews%2FThe-Lancet-Infectious-Diseases-Commission-on-Antibiotic-Resistance-Nov2013.pdf&usg=AFQjCNFic_YA8V5ZaMdLjVz8sx0_XRk-yg. (Accessed May 2015).
2. World Health Organization (2014). Antimicrobial resistance: global report on surveillance. World Health Organization. http://www.who.int/drugresistance/documents/surveillancereport/en/. (Accessed May 2015).
3. van Wyk H. (2015). Antibiotic resistance. South African Pharmaceutical Journal 2015; 82(3): 20–23. http://www.sapj.co.za/index.php/SAPJ/article/view/1977. (Accessed August 2015).
4. Todar K. (2011). Bacterial resistance to antibiotics. Todar's Online Textbook of Bacteriology [homepage on the Internet]. http://textbookofbacteriology.net/resantimicrobial_3.html. (Accessed June 2015).
5. Asín-Prieto E, Rodríguez-Gascon, A, Isla A. (2015). Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. Journal of Infection and Chemotherapy 2015; 21: 319–329. https://www.researchgate.net/publication/272200270_Applications_of_the_PharmacokineticPharmacodynamic_PKPD_Analysis_of_Antimicrobial_Agents. (Accessed Sep 2015).
6. Sweidan M, Zhang Y, Harvey K, et al. (2005). Proceedings of the 2nd national workshop on rational use of antibiotics in China. Beijing: Beijing Children's Hospital. http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiXy6Xu-7jJAhXIfRoKHZ92A_oQFggaMAA&url=http%3A%2F%2Fwww.haiasiapacific.org%2Fwp-content%2Fuploads%2F2014%2F03%2FAntibiotics-Rational-Use-report-China-2005.pdf&usg=AFQjCNHlZNydjgE4KlGt8YyESuTtvyRBCg&bvm=bv.108194040,d.d2s. (Accessed May 2015).
7. Smith R, Coast J. (2013). The true cost of antimicrobial resistance. British Medical Journal 2013; 346: 1493. http://www.bmj.com/content/346/bmj.f1493.full.pdf+html. (Accessed May 2015).
8. Wasserman S, Boyles T, Mendelson M. (2014). A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2014 Published on Behalf of the South African Antibiotic Stewardship Programme (SAASP). http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwjzqouL_rjJAhVBRBoKHcFiAoEQFggaMAA&url=http%3A%2F%2Fwww.sahivsoc.org%2Fupload%2Fdocuments%2FGuide%2520to%2520Antibiotice%2520prescribing%2520for%2520adults%2520in%2520SA_2014.pdf&usg=AFQjCNEj557V4bGhOHld6OK49HSTa0Qrdw. (Accessed May 2015).
9. Galar A, Leiva J, Espinosa M, et al. (2012). Clinical and economic evaluation of the impact of rapid microbiological diagnostic testing. Journal of Infection 2012; 65(4): 302–309. http://www.journalofinfection.com/article/S0163-4453(12)00163-6/abstract?cc=y=. (Accessed May 2015).
10. Kerremans JJ, Verboom P, Stijnen T, et al. (2008). Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. J Antimicrob Chemother 2008; 61: 428–35. http://www.ncbi.nlm.nih.gov/pubmed/18156278. (Accessed May 2015).
11. Cantón R, Morosini MI. (2011). Emergence and spread of antibiotic resistance following exposure to antibiotics. FEMS Microbiol Rev 2011; 35: 977–91. http://femsre.oxfordjournals.org/content/35/5/977.long. (Accessed May 2015).
12. Kumar A, Roberts D, Wood KE, et al. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determination of survival in human septic shock. Crit Care Med. 2006 Jun; 34(6):1589–96. http://www.ncbi.nlm.nih.gov/pubmed/16625125. (Accessed May 2015).
13. National Health Service Antibiotic Management Team. (2012). Adult IV to Oral Antibiotic Switch Therapy Guidelines. http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=13&ved=0ahUKEwiy9-3wzcXJAhWEthoKHZ7SB4k4ChAWCCQwAg&url=http%3A%2F%2Fwww.dgprescribingmatters.co.uk%2Fdocuments%2FIntravenous%2520to%2520oral%2520guidelines.pdf&usg=AFQjCNEuvgJM5zUwXkHi8PGvk0K1XSrsDQ. (Accessed May, 2015).
14. Downie L, Armiento R, Subhi R, et al. (2013). Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics-systematic review and meta-analysis. Arch Dis Child 2013;98:146–54. http://adc.bmj.com/content/98/2/146.full. (Accessed May 2015).
15. Papadakis MA, McPhee, Rabow SJ. (2013). Current Medical Diagnosis and Treatment 2013. 52nd Ed. The McGraw-Hill Campanies, Inc. New York.
16. Goossens H, Ferech M, Stichele RV, Elseviers M. (20015). Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365: 579–87. http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0ahUKEwjs8a3ZhrnJAhWHuhoKHUJmBFkQFggiMAE&url=http%3A%2F%2Fwww.wido.de%2Ffileadmin%2Fwido%2Fdownloads%2Fpdf_arzneimittel%2Fwido_arz_ESAC_Lancet_paper_0505.pdf&usg=AFQjCNFYgeOQUXuITbigCo7JkySmYinaHA. (Accessed May 2015).
17. Goodman C, Faulkner E, Gould C, et al. (2005). The value of diagnostics innovation, adoption and diffusion into health care. The Lewin Group Reports. July 2005. http://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwj9-4uxiLnJAhUE0hoKHemIDAYQFggaMAA&url=http%3A%2F%2Fadvameddx.org%2Fdownload%2Ffiles%2FLewin%2520Value%2520of%2520Diagnostics%2520Report.pdf&usg=AFQjCNEbELVVJ2CpCWLPzJKqjp2tl2aQ5Q. (Accessed May 2015).
18. National Department of Health, South Africa. (2012). Standard Treatment Guidelines and Essential Medicines List: Hospital Level: Adults. Pretoria, South Africa: Essential Drugs Programme.
19. National Department of Health, South Africa. (2013). Standard Treatment Guidelines and Essential Medicines List: Hospital Level: Paediatrics. Pretoria, South Africa: Essential Drugs Programme.
20. Rossiter D. (2015). South African Medicines Formulary. 11th Ed. The Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town.
21. Department of Health, South Africa. (2013/4). Primary Care 101 Guideline 2013/2014. Symptom-based integrated approach to the adult in primary care. Pretoria, South Africa: National Department of Health.
22. Department of Health, South Africa. (2014). Guidelines for the care of all newborns in district hospitals, health centres and midwife obstetric units in South Africa.