REVIEW OF ANTIBIOTIC PRESCRIPTION PATTERN IN OSTEOMYLITIS THERAPY AT NATIONAL ORTHOPEDIC HOSPITAL, ENUGU

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ABSTRACT

Granted that antibiotics form a major part of drugs used in the management of osteomylitis, there is a crucial need for the rational use of such drugs to maximize benefits and at the same time minimize common side effects from such drugs. This work, therefore, aimed at studying the prescription pattern to see if it is in line with accepted principle for antibiotic therapy. Prescriptions made on patient's folders within a period of eight years (from January 2005 to December 2012) were assessed retrospectively. By the permission of the hospital authority, the folders of 2400 patients who suffered from osteomyelitis within the stipulated period of 8 years were assessed, and the data on prescription pattern were analyzed. A huge amount of prescriptions were made without laboratory investigations to confirm the infecting organism. Some prescriptions did not have adequate dose regimens, and some others were not considered best for the infecting organisms. However, a few prescriptions were considered rational and adequate following the accepted principles for antibiotic therapy. A rational use of antibiotics is very crucial in the effective management of osteomylitis. This is due to the fact that bacteria are largely implicated in this health condition. Adequate use of this group of drugs entails having a broad knowledge of their properties, indication, and mechanisms of action. Physicians and pharmacists are therefore called to always abide by the accepted principles for antibiotic prescription and use.

Key Words: Review, antibiotic therapy, National Orthopaedic, Hospital.

INTRODUCTION

Osteomyelitis is a medical term signifying inflammation of osseous tissue and bone marrow as a result of infections. These infections are usually caused by bacteria, including mycobacteria, but sometimes caused by fungi (Lazzarini, et 2005). This medical condition occurs most commonly in young children and in older people, but all age groups are at risk. It is also more likely to occur in people with serious medical conditions, especially ones that depress the immune systems (Lipsky, et al 2004).

When a bone becomes infected, the soft inner part called the bone marrow often swells. As the swollen tissue presses against the rigid outer wall of the bone, the blood vessels in the bone marrow may become compressed, which reduces or cuts off the blood supply to the bone. Without an adequate blood supply, parts of the bone may die. The infection can also spread outward from the bone to form collections of pus in adjacent soft tissues, such as the muscles (Tice, et al 2003).

Bones, which usually are well protected from infections, can become infected through three major routes;

- the bloodstream which may carry an infection from another part of the body to the bones,
- direct invasion/infection, and
- infections in adjacent bone or soft tissues (Zalavras, et al 2004).

Osteomyelitis usually occurs in the ends of leg and arm bones in children and in the spine in adults, particularly in older adults. People who undergo kidney dialysis and those who inject illegal drugs are particularly susceptible to vertebral osteomyelitis.

Bacteria or fungi spores may infect the bone directly through open fractures, during bone surgery, or from contaminated objects that pierce the bone. *Staphylococcus aureus*, a member of the normal flora found on the skin and mucous membranes, is the bacteria most commonly responsible for this disease condition both in adult and children. Bloodstream-sourced osteomyelitis is seen most frequently in children, and nearly 90% of cases are caused by *Streptococcus aureus*. *Mycobacterium tuberculosis* can also infect the vertebrae to cause osteomyelitis. In patients with sickle cell disease, the most common causative agent is *Salmonella*, with a relative incidence more than twice that of *S. aureus* (Lalani, 2012). In adults, the most common form of the disease is caused by injuries exposing the bone to local infections. Here also S. aureus is the most common organism seeded from areas of contagious infections (Klevens et al, 2007). However, anaerobes and Gram-negative organisms, including *Pseudomonas aeruginosa*, *Escherichia coli*, and *Serratia marcescens*, are also common. The two most common mycotic infections in this disease condition include *Blastomyces dermatitidis* and *Coccidioides immitis* (Carek, et al 2001).

Osteomyelitis may also occur where a piece of metal has been surgically attached to a bone, as is done to repair hip or other fractures. This disease condition can occur to the skull through a spread from a sinus, gum or tooth infections. Once the bone is infected, leukocytes enter the infected area, and in their attempt to engulf the infectious organisms, release enzymes that lyse the bone. Pus spreads into the bone's blood vessels, impairing their flow, and the formation of sequestra becomes the basis of a chronic infection (Kumar et al, 2007). Often the body tries to create new bone around the area of necrosis and is called an involucrum. Osteomyelitis is an infective process that encompasses all of the bone (osseous) components, including the bone marrow. When it is chronic, it can lead to bone sclerosis, abnormal bone remodeling, and consequent deformity.

Some other risk factors to this disease condition include diabetes, peripheral artery disease, chronic joint disease, alcoholism, intravenous drug abuse, chronic steroid use, immunosuppression, tuberculosis, HIV and AIDS, and sickle cell anaemia (Schinabeck, Johnson, 2005).

Chronic osteomyelitis carries high risk of complication, often due to the presence of intracellular bacteria inside bone cells, that are difficult to eradicate. Most antibiotics find it difficult to gain easy access inside the bone, making room for antibiotic failure and development of resistance. This event results in significant cost and disability, potentially leading to amputation (Zalavras, 2004). Intracellular existence of bacteria in osteomyelitis is likely an unrecognized contributing factor to its chronicity (Baer, William, 1931).

Signs and symptoms—onset of acute osteomyelitis is usually rapid, with sudden pain in the affected bone. There is also tenderness, heat, swelling, and restricted movement over the area. Associated systemic signs and symptoms include tachycardia, sudden fever, and malaise (Berbari, 2009). Generally, the signs and symptoms of both chronic and acute osteomyelitis are the same, except that chronic infections can persist intermittently for years, flaring up spontaneously after minor trauma. Sometimes, however, the only symptom of chronic infection is the persistent drainage of pus from an old pocket in a sinus tract.

Diagnosis— in practice, several diagnostic modalities are used to determine the presence of osteomyelitis and these include laboratory investigations, radiographic imaging, radionuclide studies, and cross-sectional imaging. The gold standard for diagnosing osteomyelitis is bone biopsy and culture tests. Proper and early diagnosis of this clinical condition is very crucial in its efficient management (Jaberi, 2002).

Management— the most common treatments for osteomyelitis are antibiotics, and surgery to remove portions of bone that are infected or dead, and in either of the treatments, hospitalization is necessary. Surgical debridement is the mainstay of treatment; it removes the necrotic tissue and provides an infection-free scaffold for future healing. If surgery is not possible, indefinite antimicrobial therapy may be required but this is generally accepted to be less effective than surgery (Lamp et al, 2007). The use of hyperbaric oxygen therapy may help get more oxygen to the bone and promote healing. This is done using a pressure chamber that resembles a large clear tube.

Antibiotics, which form the pivot of osteomyelitis drug treatment, refer to substances produced by microorganisms, or to similar substances (produced wholly or partly by chemical synthesis), which in low concentrations inhibit the growth of

other microorganisms (Calderon, Sabundayo, 2007). According to Benedict and Langlykke (1947), an antibiotic is a chemical compound derived from or produced by a living organism which is capable in small concentrations of inhibiting the life processes of microorganisms. There are over 100 antibiotics prescribed in modern medicine, but the majority is derived from seven main classes that are widely used today. They include penicillins, cephalosporins, macroclides, fluoroquinolones, sulfonamides, tetracyclines and aminoglycosides. Each of these groups has different properties with regards to their indications, mechanisms of actions, contra-indications and side effects. For effective management of osteomyelitis, there is need for a careful consideration of the properties of these agents to decide which antibiotic is selected among others for different patients with this disease condition.

Generally speaking, antibiotics are indicated in the management of diseases conditions caused by bacteria or certain fungi; they are not effective against viruses. Antibiotics either kill microorganisms (bacteriocidals) or stop them from reproducing (bacteriostatics), allowing the body's natural defenses to eliminate them (Mark, 1997). They actually observe the "magic bullet concept", which is a chemotherapeutic concept whereby the antimicrobial agents selectively attack the microorganisms and other cancer cells in the body without affecting the host's cells. However, antibiotics in practical usage have some side effects which can be accommodated by the individual using them. Some of these side effects include stomach upset, diarrhea, allergies, and in women, vaginal yeast infection due to imbalance in the vaginal micro-flora. Antibiotics can also interfere with entero-hepatic circulation of certain drugs which may result in therapeutic failure of such drugs (Miller et al, 1994). Some side effects are more severe and, depending on the antibiotic, may disrupt the function of the kidneys, liver, bone marrow, or other organs. Blood tests are used to monitor such adverse reactions in other to make necessary interventions (Shehab, et al, 2008).

Surgery, which is very important in the management of some forms of this bone disease, depends on the severity of the infection, and osteomyelitis surgery may include one or more of the following procedures:

- Draining of the infected area— involves opening the area around the infected bone and draining any pus or fluid that has accumulated in response to the infection.
- Removing diseased bone and tissue— in a procedure called debridement, the surgeon removes as much of the diseased bone as possible. Surrounding tissues that shows signs of infection also may be removed.
- Restoring blood flow to the bone— sometimes, blood flow to the diseased bone may be hampered especially after procedures like debridement. Here, the surgeon ensures efficient blood flow to the bone which is very necessary for healing.
- Removal of foreign objects— in some cases, foreign objects, such as surgical plates or screws placed during a previous surgery, may have to be removed.
- Amputation— as a last resort, surgeons may amputate the affected limb to stop the infections from spreading further in the bone and to other parts of the body.

Complications

Although osteomyelitis is often treated successfully, severe and chronic cases can lead to other problems. Some of these complications include;

- Bone death (osteonecrosis)— osteomyelitis can impede blood circulation within the bone, resulting to bone death. Although osteonecrosis of a small portion of the bone can be ignored and the patient manages to live a near-normal life, involvement of a large section of the bone may necessitate amputation of that limb to prevent spreading of the infection.
- Bone abscess— this is the formation of an enclosed liquefied tissue called pus, within the bone. It is one the most common complications of osteomyelitis, and it occurs due to the body's defensive reactions to the invading microorganism (Kanoun et al, 2007).
- Bacteraemia— this is the condition of the presence of bacteria in the blood. Blood under normal condition is a sterile medium, hence the presence of bacteria in it is a medical condition that needs attention. Bacteraemia is a possible complication of osteomyelitis where the causative bacteria gain access to the blood.
- Septic arthritis— in some cases, infections within the bones can spread into a nearby joint, resulting in arthritis and other joint problems.
- Amputation— this is often used as a last resort for treating chronic osteomyelitis, especially if the blood supply to the bones is severely reduced. With a reduced blood supply, the bones receive fewer infection-fighting blood

cells. This makes the infection to spread beyond the bone and into the surrounding soft tissue. The tissue then begins to die resulting in gangrene formation which normally necessitates amputation.

- Impaired growth— in children, the most common location for osteomelitis is in the softer area called growth plates, at the either ends of the long bones of the arms and legs. When this happens, normal growth may be interrupted in the infected growth. Impaired growth is often not a problem in adults.

METHODS

A total of 2400 patients' folders at the National Orthopedic Hospital, Enugu. These folders were selected for the study, were those of the patients who were treated for osteomyelitis in the hospital. These folders selected for the study were those of the patients who were treated for osteomyelitis in the hospital between the year 2005 and 2012. The folders were critically assessed to extract data on the prescription patterns of antiobiotics. This retrospective study was conducted for a period of 20 days within the folders' room of the hospital.

Ethical approval was got from the hospital management board before we could handle the patients' folders. The data obtained were analyzed using the statistical technique : the percentage method of analysis, with level of significance placed at $p \leq 0.05$. The choice of the method was influenced by the fact that was found most useful in analyzing the data collected in this study.

RESULTS

Table 1 and 2 below show the frequency of prescription of antibiotics in the management of osteomyelitis. The tables show different classes of antibiotics with their representative drugs. The number of prescriptions of these antibiotics in each of the years of the study was represented. The summations of the prescriptions for the eight years were also presented as shown below.

Table 1: Annual Frequency of prescription of Antibiotics

CLASS OF ANTIBIOTICS	ANTIBIOTICS	FREQUENCY OF PRESCRIPTIONS								
		2005	2006	2007	2008	2009	2010	2011	2012	Total
Aminoglycosides	Gentamicin Streptomycin	280 140	300 -	250 -	1100 -	360 -	550 -	400 -	1080 -	4320 140
Penicillins	Crystalline Penicillin Ampicillin/Cloxacillin Amoxacillin/Clavunate Flucloxacillin Ampicillin	- 910 70 70 -	- 1000 700 - -	- 606 450 - -	- 1050 750 - 50	- 240 540 - 60	- 102 550 - 70	- 160 105 - -	- 180 1170 - -	- 4248 4335 950 180
Macrolide	Erythromycin Azithromycin Vancomycin	790 - -	700 - -	250 - -	700 50 -	723 - -	605 - -	213 - -	52 - -	4033 50 -
Tetracycline	Minocycline	-	-	50	-	-	-	-	-	50
Imidazole	Metronidazole	210	403	650	700	720	1700	1280	1770	7433
Sulphonamide	Cotrmoxazole	70	200	100	50	-	100	40	53	613
Quinolones	Ofloxacin Perfloxacin Ciprofloxacin Levofloxacin	70 - 490 -	50 150 1250 -	100 - 2350 -	150 300 800 -	180 306 780 27	301 151 1750 60	720 - 1280 46	1260 212 2160 37	2831 1119 10860 170
Lincomycins	Clindamycin	-	50	500	650	240	102	323	1350	3215
Cephalosporins	Cefuroxime Ceftriaxone Cephalexin Ceftazidim (Fortum)	70 - - -	250 - - -	150 100 - -	250 100 - -	300 - - 25	253 - 51 46	341 - 704 28	2340 2250 375 -	3954 2450 1130 9 9
Antituberculosis	Rifampicin	210	150	400	305	253	411	168	-	1897
	Total	3380	5203	5956	7005	4754	6802	6688	14289	54077

Table 2: Percent frequency of prescriptions

CLASS OF ANTIBIOTIC	ANTIBIOTIC	PERCENTAGE (%) ANNUAL FREQUENCY OF PRESCRIPTIONS								
		2005	2006	2007	2008	2009	2010	2011	2012	Mean%
Aminoglycoside s	Gentamicin Streptomycin	8.25 4.14	5.37 0	4.20 0	15.70 0	7.57 0	8.46 0	5.98 0	7.56 0	8.00 0.52
Penicillins	Crystalline. Penicillin Ampicillin/Cloxacillin Amoxicillin/Clavunate Flucloxacillin Ampicillin	0 26.92 2.07 2.07 0	0 19.22 13.45 0 0	0 10.17 7.56 0 0	0 14.99 10.71 0 0.71	0 5.05 11.36 0 1.26	0 1.52 8.46 0 1.08	0 2.39 1.57 13.16 0	0 1.26 8.19 0 0	0 10.19 7.92 1.90 *0.38
Macrolides	Erythromycin Azithromycin Vancomycin	23.37 0 0	13.45 0 0	4.20 0 0	9.99 0.71 0	15.21 0 0	9.30 0	3.18 0 0	0.36 0 0 0	9.88 0.09 0
Tetracyclines	Minocycline	0	0	0.84	0	0	0	0	0	0.11
Imidazoles	Metronidazole	6.21	7.75	10.91	9.99	15.15	26.15	19.14	12.39	13.46
Sulphonamides	Clotrimoxazole	2.07	3.84	1.68	0.71	0	1.54	0.59	0.37	1.35
Quinolones	Ofloxacin Perfloxacin Ciprofloxacin Levofloxacin	2.07 0 14.50 0	0.96 2.88 24.02 0	1.68 0 39.46 0	2.14 4.28 11.42 0	3.79 6.44 16.41 0.57	4.63 2.32 26.91 0.92	10.76 0 19.14 0.69	8.82 0.15 15.12 0.26	4.36 2.01 20.99 0.30.
Lincomycins	Clindamycin	0	0.96	8.39	9.28	5.05	1.57	4.83	9.45	4.94
Cephalosporins	Cefuroxime Ceftriaxone Cephalexin Cephtazidime(Fortume)	2.47 0 0 0	4.80 0 0 0	2.52 1.68 0 0	3.57 1.43 0 0	6.31 0 0 0.53	3.89 0 0.78 0.71	5.10 0 10.53 0.42	16.38 15.75 2.68 0	5.63 2.36 1.74 0.21
Antituberculosis	Rifampicin	6.21	2.88	6.72	4.35	5.32	6.32	2.51	0	4.29

Table 3: Laboratory investigations

Total No of cases	Total No of cases with laboratory investigation	Total No of cases without laboratory investigation	% No of cases with laboratory investigations	% No of cases with prescriptions written before lab investigations	% No of cases with prescription written after laboratory investigations
2400	1425	975	59.38	40.06	1.02

DISCUSSION

Osteomyelitis is a disease condition that needs radical as well as rational treatment to eradicate the causative agents and as such avoid certain complications that may come up in the course of the disease, especially antibiotic resistance. Certain drugs, such as analgesics, anti-inflammatory agents, hematinics, antibiotics, etc, form the regimen used in the effective management of this condition. Prominent among these regimens are the antibiotics which kill bacteria or halt the growth of the major causative agents involved in the pathogenesis of the disease condition.

Although very essential in the treatment, antibiotics are a group of drugs that have a wide range of side effects in the human body, and as such need utmost rational approach in the usage. This approach is very important, first, to optimize treatment, and secondly to minimize side effects of these drugs to the body. The rational use of antibiotics in this area of treatment involves using the best antibiotic for the specific causative agent at the required dose and duration.

In Table 1 above, different classes of antibiotics were used in the treatment, with ciprofloxacin, a member of quinolone antibiotics, having the highest frequency (10860) of prescriptions in the eight years of study with mean frequency of 20.99% (Table 2), though the difference is not significant $p \geq 0.05$. The high frequency of this drug is expected due to the crucial role it plays in the management of osteomyelitis, and this is reflected in the work by Chin, and Neu (1984). The results available in Table 1 also reveal that many prescription cases (4320) with mean frequency (8.0%; Table 2) involved gentamycin, an aminoglycoside antibiotic. Although this is a potent antibiotic, its common side effects which include renal and ototoxic side effects seemed not considered in this treatment. Other efficient and less toxic antibiotics such as cephalosporins, would have been more appropriate. Crystalline penicillin was not used at all, perhaps due to the common causative organisms not being responsive to this antibiotic. Ampicillin/Cloxacillin combination was significantly prescribed by the doctors during the period of study to the tune of 4824 prescriptions (Table 1), yielding mean frequency of 10.19%, as shown in Table 2. This also showed the crucial role this drug plays in the management of osteomyelitis.

Metronidazole, in Table 1, had the second highest percentage prescriptions of 7433, yielding mean frequency score of 13.46% in Table 2. Again, the difference was not significant $p \geq 0.05$.. This also showed the crucial role this drug plays in the management of osteomyelitis. Metronidazole is very sensitive to anaerobic organisms, which are often implicated in osteomyelitis. Secondly, metronidazole is a cost-effective agent which has been used for the treatment of infections for more than 45 years and is still successfully used for the treatment of trichmoniasis, amoebiasis, and giardiasis (Spellberg, Lipsky, 2012). Anaerobic bacterial infections caused by Bacteroides species, fusobacteria, and clostridia respond favourably to metronidazole therapy.

It was observed in Table 3 that a good number of cases (975), yielding 40.6%, were attended to blindly without laboratory investigations. According to Spellberg and Lipsky (2012), it is usually appropriate to delay treatment until culture and sensitivity test is done and the results obtained. This is particularly important in chronic osteomyelitis, unless the infection is severe, in which case empirical treatment is started before laboratory results arrive afterwards. It is expected that the treatment pattern adjusts whenever results are available to capture the causative organisms. Blind treatment could lead to treatment failure, bacterial resistance and increased chances of complications. Proper laboratory investigations have been known to ensure adequate management of this clinical condition (Jaberi, et al, 2002).
However, it was observed in the Table 3 that 1.02% of the cases followed the recommended pattern of treatment as spelt out by Spellberg and Lipsky (2012) above, indicating that many of the prescribers did not follow standard treatment guidelines.

RECOMMENDATIONS

Treatment of osteomyelitis using antibiotics requires a systematic approach in other to maximize therapy. Antibiotic treatment should be based on the identification of causative pathogens from bone cultures at the time of bone biopsy or debridement. The normal steps, especially for acute cases, requires that bone culture samples are obtained first on admission of the patient, then suspected pathogens are covered by initiation of a parenteral antimicrobial treatment pending the outcome of the laboratory results. However, treatment should be modified once the laboratory results are available and the specific causative organisms identified. Parenteral and oral antibiotics may be used alone or in combination depending on microorganism sensitivity results, patient compliance and dispositions, as well as the overall progress of the therapeutic regimens. NOHE and other hospitals rendering such medical services should harmonize their level of practice to follow the standard treatment practice as mentioned above. Normal antibiotic treatment consists of a 4 to 6 week course, as it has been shown through animal studies and observations that bone revascularizations after debridement takes a minimum of 4 weeks. These recommendations, including the duration of antibiotic treatment, should be strictly observed for maximum therapeutic outcomes.

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