SURVEY OF EMPIRIC ANTIMICROBIAL THERAPY FOR COMMON PEDIATRIC INFECTIONS

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INTRODUCTION

Infectious diseases remain the leading cause of childhood mortality and morbidity in developing countries despite the advent of antimicrobial use. Socioeconomic factors such as poverty and associated conditions of malnutrition, overcrowding, ignorance, poor sanitation and the failure of governments to provide adequate health care delivery constitute the background for the development of serious childhood infectious diseases. In third world countries such as the Philippines, where severe infectious diseases and bacterial etiologies are predominant, antimicrobial use is widespread and concomittant antibiotic resistance is high. These circumstances dictate that antimicrobials be used in a rational and appropriate manner.

In the Philippines, the presence of antibiotic misuse and abuse has long been recognized. However, it is only in recent years that steps have been taken to assess the magnitude of the problem and provide some solutions. Among the first programs launched by the Department of Health (DOH) to disseminate information and provide training to physicians and health care personnel were the Control of Diarrheal Diseases (CDD) and the Control of Acute Respiratory Infections (CARI) along with the establishment of national drug policies. Admittedly, the process is a long and tedious one with an equally difficult task of evaluating outcomes.

ANTIBIOTIC USE

Studies on antibiotic use in our country show that as much as 25.1% of prescriptions are for antimicrobials compared to less than 14% in countries such as USA, UK, Brazil and Japan. Drug consumption patterns studied in 1989 revealed that 20% of drugstore purchases were for antibiotics and 66% were without prescriptions. In 1990, Lansang et al. determined the frequency of purchase by type of antibiotics and aminopenicillins topped the list at 28.4%. Other antibiotics purchased were anti-TB drugs 14%, natural penicillins 11%, tetracycline 8.2%, antidiarrheals (which were most frequently purchased without prescription) 7%, macrolides 6.8%, chloramphenicol 3.5%, and cephalosporins 2.2%.

MATERIALS AND METHODS

This study was conducted to determine the most commonly used antibiotics for the empiric treatment of childhood infections. Previously, it has been shown that antibiotics are largely used empirically without any definite pathogen being isolated or identified not only in hospitalized patients but more so in ambulatory cases. The lack of adequate facilities and well-trained personnel in both urban and rural areas plus the high cost of isolation and culture prevent the proper identification of pathogens in a large majority of patients.

There were 91 respondents to 200 questionnaires randomly distributed to pediatricians from all over the country while attending an Infectious Disease Meeting. They were made to rank according to preference and actual use a listing of antibiotics for various infections. They were also made to indicate and write down their preferences if these were not included in the list. About 75% of the respondents were practising in urban hospitals and clinics with majority of their patients belonging to the middle income bracket.

RESULTS

The results of this study are summarized in Table 1.

ACUTE RESPIRATORY INFECTIONS

For acute otitis media, 56% of respondents chose amoxicillin as their first line drug followed by cotrimoxazole in 28.5%, coamoxiclav (12%) and erythromycin (7.6%). Procaine penicillin, a first line drug recommended by the DOH was not included in the list. Likewise, in acute exudative tonsillopharyngitis, there is a general agreement to choose oral penicillin followed by amoxicillin, erythromycin and cotrimoxazole but not benzathine penicillin which is among the recommended drugs. The newer macrolides are also being considered by a few although studies on their use in children are still ongoing.

As for community-acquired childhood pneumonia, the influence and extent of the WHO-DOH CARI program is shown by the use of penicillin G and chloramphenicol by almost 60% of the respondents in the treatment of severe pneumonia. Alternative drugs are ampicillin and gentamicin (22%), second generation

Table 1. First and alternative choices for the empiric antibiotic treatment of common infections.

	Infection	First Choice	Alternatives
1.	Acute otitis media	Amoxicillin	Cotrimoxazole Coamoxiclav Erythromycin
2.	Exudative tonsillo pharyngitis	Oral Penicillin	Amoxicillin Erythromycin Cotrimoxazole Clarithromycin
3.	Pneumonia, community-acquired mild-moderate below 5 years.	Cotrimoxazole Amoxicillin	Oral penicillin
	Pneumonia severe	Chloramphenicol Penicillin G	Ampicillin + gentamicin
4.	Pneumonia, community-acquired mild-moderate above 5 years.	Cotrimoxazole Oral Penicillin	Cephalexin Coamoxiclav
	Pneumonia severe	Penicillin G	Chloramphenicol Ceftazidime
5.	Pneumonia hospital-acquired	Ceftazidime + gentamicin	Ceftazidime + oxacillin
6.	Lung abscess/empyema	Oxacillin	Nafcillin Metronidazole + oxacillin Coamoxiclav Cephalothin Vancomycin
7.	Acute bacterial meningitis	Ampicillin + chloramphenicol	Ampicillin Chloramphenicol
8.	Brain abscess	Penicillin + chloramphenicol	3rd generation cephalosporin Metronidazole Oxacillin
9.	Endocarditis	Penicillin	Oxacillin Gentamicin
10.	Acute watery diarrhea	Cotrimoxazole	Metronidazole
11.	Acute bloody diarrhea	Cotrimoxazole	Metronidazole
12.	Peritonitis primary	3rd generation cephalosposrin + metronidazole	Penicillin G + aminoglycoside Ampicillin + aminoglycoside Ceftazidime
13.	Peritonitis with intra-abdominal infection surgery	Ampicillin + metronidazole + aminoglycoside	Ceftazidime + metronidazole
14.	Urinary tract infection	Cotrimoxazole	Amoxicillin Aminoglycoside
15.	Urinary tract infection hospital-acquired	Aminoglycoside	3rd generation cephalosporin 2nd generation cephalosporin Chloramphenicol
16.	GC urethritis	Penicillin Ceftriaxone	Quinolones
17.	Skin infections	Oxacillin	Oral penicillin
18.	Osteomyelitis	Oxacillin	3rd generation cephalosporin
19.	Sepsis neonatorum	Ampicillin + aminoglycoside	Oxacillin + aminoglycoside

cephalosporins (21%) and third generation cephalosporins (20%). Likewise, in the out-patient treatment of community-acquired pneumonia, cotrimoxazole or amoxicillin (88%) were the usual first choice followed by oral penicillin, first generation cephalosporins and coamoxiclav.

In hospital-acquired pneumonia, combination therapy is the rule with 60% favoring the use of ceftazidime plus either gentamicin (38%) or oxacillin (24%). The rest of the choices were for cefuroxime and the combination of piperacillin and gentamicin. A smaller percentage chose monotherapy with either ceftazidime or imipenem. The WHO recommends the least expensive aminoglycoside (gentamicin) and benzyl penicillin or a first generation cephalosporin. The use of imipenem in children is still undergoing evaluation. One must bear in mind that the empiric choice of antibiotics for hospital-acquired infections are largely based on the existing hospital flora.

Oxacillin is the first choice in the treatment of lung abscesses/empyemas (45%). Alternatives included nafcillin, metronidazole plus oxacillin, coamoxiclav, cephalothin and vancomycin.

CNS INFECTIONS

In acute bacterial meningitis, 86% use a combination of ampicillin and chloramphenicol while the rest chose ampicillin (8%) or chloramphenicol (5%) alone. Local guidelines recommend the use of chloramphenicol alone.

Brain abscesses are usually treated with a combination of penicillin and chloramphenicol by 41%. Alternatives were ceftazidime, metronidazole and amoxicillin.

ENDOCARDITIS

Penicillin G is the most commonly used antibiotic in the treatment of native valve endocarditis in 64%. About 18% would either give gentamicin or oxacillin as

alternatives. However, the rest of the respondents indicated that they had limited experience in the treatment of endocarditis.

GASTRO-INTESTINAL INFECTIONS

About 44% of respondents would not treat acute watery diarrhea with any antibiotics, however, a larger percentage 56% would rather give antibiotics: either cotrimoxazole or metronidazole. The DOH-CDD recommendations focus on hydration rather than antibiotic therapy. For bloody diarrhea, cotrimoxazole (59.3%) is the first line drug followed by metronidazole (32%) as an alternative.

A combination of a third generation cephalosporin plus metronidazole was the first choice for the treatment of primary peritonitis while penicillin plus an aminoglycoside was the second in 37% and 32% of respondents respectively. The WHO recommends penicillin as first line drug for primary peritonitis. On the other hand, for peritonitis associated with intra-abdominal infection or surgery, ampicillin with metronidazole and an aminoglycoside were chosen by 45%, while 23% would rather give ceftazidime and metronidazole. About 20% indicated their limited experience in the management of such cases.

GENITO-URINARY TRACT INFECTIONS

Among the antimicrobials listed, cotrimoxazole is used by 77% for the treatment of urinary tract infections while a few give amoxicillin (12%) or an aminoglycoside (9%). Hospital-acquired urinary tract infections are usually treated with an aminoglycoside (61%) while 21% would give a third generation cephalosporin. Others chose a second generation cephalosporin or chloramphenicol as alternatives.

Special consideration was made for gonococcal urethritis where penicillin (27%) and ceftriaxone (25%) are used almost with equal frequency. Quinolones were considered by 16% as alternative. The rest had limited experience in the treatment of sexually transmitted diseases.

SKIN AND SUBCUTANEOUS INFECTIONS

Oxacillin (89%) was the choice of the majority with penicillin (6%) as an alternative considered by a few for the treatment of skin infections.

OSTEOMYELITIS

Oxacillin was chosen as the first-line drug by 74% with third generation cephalosporin as an alternative for the treatment of osteomyelitis.

NEONATAL SEPSIS

For neonatal sepsis, 84.6% chose the combination of ampicillin and gentamicin. Alternatives included oxacillin plus an aminoglycoside or a 3rd generation cephalosporin.

DISCUSSION

The results of this study further elucidates the need for a well-defined antibiotic policy to be included in a comprehensive health program. These standards are necessary and perhaps will serve to minimize the emergence of antibiotic resistance. The DOH has formulated such guidelines and is in the process of implementing them. The provision consists of the establishment of a Therapeutics Committee in each regional area or institution which will: 1) formulate prescribing strategies appropriate for their circumstances, 2) audit antibiotic use, 3) organize appropriate educational measures, and 4) recognize the forces influencing prescribing doctors.

It is recommended to classify antimicrobial preparations into: 1) restricted, 2) unrestricted, and 3) excluded. Revisions and peer reviews should be done periodically. The guiding principles for rational antibiotic use includes consideration of the antibiotic characteristics (spectrum of activity, efficacy, safety, etc.), restriction of prophylactic use, local epidemiological data for empiric therapy while directing antimicrobial therapy for proven pathogens.

In conclusion, the use of antimicrobials in the Philippines and other developing countries are generally more widespread due largely to the high mortality and morbidity from infectious diseases. Socioeconomic factors contribute significantly to inappropriate use of antimicrobials. Factors influencing prescribing patterns of physicians such as education, peer pressure, physician characteristics, promotional activities by drug companies and demands from patients and society are important considerations in studying antibiotic use in developing countries. It is hoped that the setting up of Therapeutics or Drug Committees will strengthen the influences that foster rational prescribing and counter those that have the opposite effect.

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2. Guideline on Rational Use of Antibiotics in the Treatment of Common Infections-Module II. Manila: Department of Health, 1992.

PROCEEDINGS OF A SYMPOSIUM...
(PIDSP Convention • September 1994)

THE IMMUNOLOGIC BASIS OF IMMUNIZATION

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1. Innate vs. Adaptive Immunity

Innate response e.g. phagocytosis and lysis of bacteria by complement are an important initial line of defense against invading pathogens. But these are non-specific, stereotypic and cannot be amplified even on subsequent exposure tot he same organism; hence the need for adaptive immunity.

Table 1. Some cells and molecules of the immune system.

	Cells	Molecules
Innate Immunity	phagocytes NK cells	complement
	B lymphocytes	antibodies
Adaptive Immunity	T lymphocytes	

Adaptive immune responses have the following features:

memory	recovery from infection by one pathogen protects against subsequent infection by the same organism ("immunity")
specificity	recovery from infection by one pathogen does not protect against another (unless the organisms are closely related)
diversity	responses can be made against a multitude of different organisms.

Vaccination or active immunization aims to elicit adaptive immunity and protect an individual from the wild-type organism even long before exposure.

Table 2. Comparison of innate and adaptive immune responses

	Ability to mount a response: Before pathogen is present	When pathogen is first encountered or (active immunization)	Y pathogen is subsequently encountered or (booster response)
innate immunity	+	+	+
adaptive immunity	–	+ (primary response)	+++ (secondary response)

2. Initiation of Adaptive Immunity

Both B and T lymphocytes develop from a pluripotent stem cell. B cells mature in the bone marrow while T cells develop in the thymus. In the thymus T cells are committed to become helper T cells (TH) or cytotoxic T cells (Tc or TLC). Majority of TH cells have the CD4 molecule on their surface while majority of Tc cells have CD8. As they leave these primary lymphoid organs they are capable of recognizing, through the receptors on their surfaces, the various structural components and products of infectious agents and other foreign material. Such substances reacting with B and T cells receptors are called antigens. The portion of the antigenic molecule which specifically binds to the receptors called the antigenic determinant or epitope. When an immune response is elicited antigens called immunogens. The encounter with antigen usually takes place in the secondary lymphoid organs e.g. the lymph nodes.

Each B cell is studded with surface or membrane-bound immunoglobulins (IgM/IgD) all of them capable of recognizing only a single epitope. T cell receptors likewise bind to a specific epitope per T cell. Genetic rearrangements during B and T cell development, however, ensure extreme diversity of B and T cell receptors O that the immune system can potentially recognize all the antigens an individual may encounter throughout his life.

When a or T cell recognizes antigen it undergoes clonal expansion but each progeny recognizes the same antigen. Clonal expansion generates, in the case of the B cell, shortlived effector cells called plasma cells which secrete immunoglobulins (antibodies) with the same specificity as the surface Ig's, and memory B cells which may last for years. This is the primary humoral immune response. Subsequent exposure to the same antigen elicits a faster, stronger, longer-lasting secondary cellular immunity.

Immune responses then depend upon antigen presentation and lymphocyte differentiation and are time-dependent.

A. Ig receptors on B cells recognize three-dimensional shapes or conformation on the exposed antigen surface. T cell receptor epitopes on the other hand could include protein sequences in the antigen interior as these may be brought out during antigen processing and displayed on the surface of the APC. B and T cells may not recognize the same epitope on a vaccine preparation.

B. Since T cell response exhibits MHC restriction, genetic control of T cell response is expected. Thus potential variations in immune responsiveness of individuals is also expected.

C. APC'c phagocytose/endocytose foreign proteins which may be non-infectious and degrades them into peptides which complex with MHC II antigens. Viruses infect other somatic cells which express class I MHC antigens and viral peptides can be presented then to CTL's. Since vaccines contain both infectious and non-infectious particles both classes of responses may be induced.

D. B cells endocytose foreign epitopes and complex them with MHC Class II antigens on their surface. TH cells (generated by the macrophage/dendritic cell pathway to the same antigen) may recognize this complex and get activated. Activated TH cells secrete chemical substances called lymphokines. A subset of T cells called TH1 secretes interleukin – 2 and interferon – gamma. IL-2 together with IL-4 from another TH subset (TH2) aid in further T cell proliferation as well. Antigens handled by the B cells in this manner called T-dependent antigens and because of TH cell help the immune response they elicit differs from T independent antigens. (Fig. 1)

The mechanism of T-dependent B cell response is better elucidated by hapten-carrier studies. A hapten is a molecule which can bind to a lymphocyte receptor but is unable to induce an immune response on its own but can do so when coupled to a carrier or conjugate protein. It may not be possible to generate responses to hapten alone because it is too small to ably associate with an MHC molecule. The carrier provides the T-cell epitope needed for TH activation. IL-4 seems to act better on resting T cells and the TH2 subset may be more important in providing T cell help.

T1 antigens can be divided into 2 types. Type 2 antigens have repeating determinants that may cross-link B cell receptors providing a signal for activation and can stimulate B cell response in adult but not neonatal mice. Type I antigens stimulate B cell response in both groups of mice.

Secondary responses are readily generated to TD antigens but not to T1 antigens. The implication is that memory T cells cannot be generated during T1 responses because T cells recognizes peptide – MHC complexes but many T1 antigens are not proteins. Capsular polysaccharides vaccines suffer from being T1 antigens but conjugating them to protein (e.g. H. influenza vaccines conjugated to tetanus toxoid) makes them TD antigens.

E. The different components of the immune response to infection/immunization arise in time dependent fashion. (Fig. 2)

Both antibody – secreting and memory B cells

Table 3. Examples of TD and T1 antigens

TD	T1-2	T1-1
proteins most	polymerised flagellin natural polysaccharides (e.g. capsular)	bacterial cell products LPS PPD of BCG
hapten-carriers most	synthetic polysaccharides dextran	polyclonal B cell activators

Figure 1. TD and T1 antibody responses in mouse.

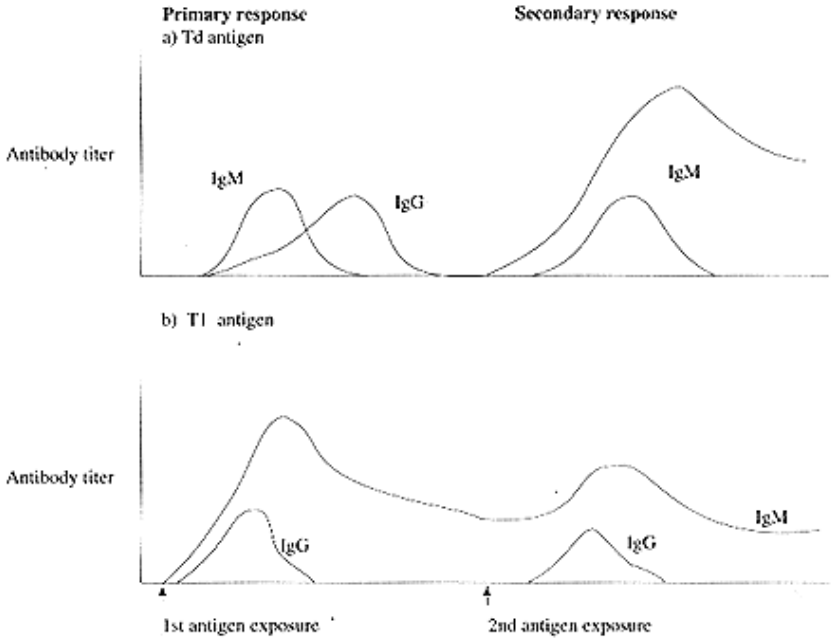
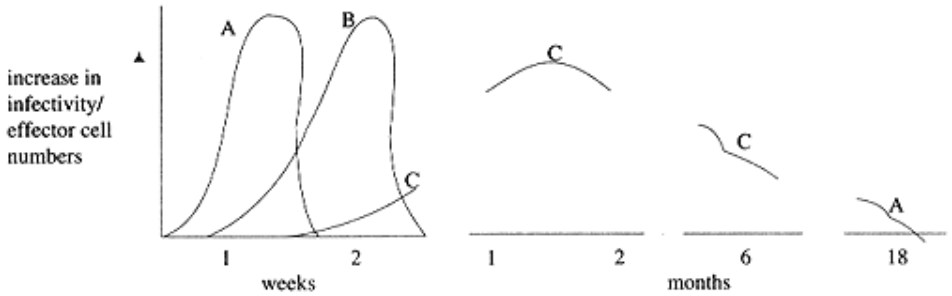


Figure 2. Time sequence of murine influenza virus infection and subsequent immune response.



time
A growth and disappearance of virus
A appearance and disappearance of T effector cells
C appearance and continuing presence of antibody-secreting cells

are present after infection. Memory B cells are continually recruited by persisting non-infectious antigen to form plasma cells. On the other hand, Tc cells persist but require further exposure to infectious virus for activation.

3. The functions of B and T cell responses

Antibodies are important:

a. They can react with a few epitope of a virus and prevent its entry into cells (virus neutralization). Such epitopes are called protective epitopes because they elicit protective, neutralizing antibodies. If the virus can change its epitopes (antigenic drift) a vaccine will be ineffective (e.g. HIV). They also neutralize toxins produced by bacteria.

b. They coat encapsulated bacteria making them easier to phagocytose (opsonization). Antibody molecules can bind at their other and (Fc) to receptors on the phagocytes. They also facilitate removal of debris.

c. They can activate complement which also severe as opsonins and chemoattractants.

Cellular immunity has 2 arms: a helper arm and a killer arm. Lymphokines from TH cells have a variety of effects on cells including those not involved in the immune response. Many of these cytokines however aid other T cells, B cells and macrophages. IF – gamma is a potent activator of macrophage intracellular killing – an important defense against intracellular bacteria. Tc cells on the other hand can directly kill (perforate) somatic cells infected by a virus or tell them to commit suicide (programmed cell death or apoptosis). They are an important defense against intracellular pathogens (e.g. viruses) which could not be reached by antibodies.

Vaccination stimulates both cellular and humoral immunity which have different functions but it is the humoral immune response which lends itself easily to measurement (antibody titers).

4. Requirements of a Vaccine

Considering all of the above, the general requirements of a vaccine to be effective are:

a. Activation of APC's to initiate Ag processing and production of lymphokines.

b. Activation of both T and B cells to give a high yield of memory cells.

c. Generation of TH and Tc cells to several epitopes. This will help overcome variation in immune response due to MHC polymorphism in the population.

d. Persistence of antigen, especially in dendritic follicular cells in contact with memory B cells, to form secreting cells.

Some illness e.g. diptheria and tetanus require only that their toxins be neutralized.

However, many infections require both humoral and cellular responses. The best vaccines are those which elicit both e.g. live virus vaccines. The antibodies produced reduce the virus load from a subsequent challenge (infection) while Tc effector cells to many epitope can destroy infected by the virus.

Vaccines made from 1 or few components of the organisms (subunit preparations) tend to induce poorer responses and need to be repeated for several doses with adjuvants to elicit an adequate response. Adjuvants tend to keep antigen at or near the injection site prolonging contact with antigen-presenting cells. An example is alum.