Repeated Antimicrobial Therapy in Children: 
The Problem of its Effectiveness and Safety

A Ten-Year Survey of the Practice of Simultaneous and 
Successive Combination Therapy*

KARL E. KASSOWITZ, M.D., F.C.C.P.**

Milwaukee, Wisconsin

The discovery of effective and powerful antimicrobial chemicals has had a twofold impact on the world. On the one hand it has substantially reduced the total number of microbial organisms by direct bactericidal action, and among the surviving pathogenes it has caused a still problematical change in their relationship to their environment.

The following investigation into the effects of repeated antibacterial therapy during 10 years at Milwaukee Children's Hospital has as its object the assessment of the actual results obtained by applying the chemotherapeutical and antibiotic agents, as they became available, by the entire attending pediatric, surgical and resident staff of our hospital, without any strict centralized overall therapeutic policy.

In evaluating this large clinical material with a great diversity of therapeutic programs and combinations we have tried to disassociate ourselves, temporarily at least, from the great temptations of overenthusiasm and of overskepticism which can be found so frequently in the literature pertaining to modern anti-infectious therapy.

The main reason for this attempt at arriving at some definite conclusions, by way of empiricism rather than scholasticism, is the appalling diversity of statements and opinions about indications and contraindications, bordering here and there on outright contradiction. The volume of literature in this particular field is such that even an approximation to a complete review is positively prohibitive. In the following paragraphs a selection of ambiguous, confusing and contradictory quotations will be given and not, to be sure, for the sake of criticism, but in order to illustrate the psychological impasse medical science is in, surrounded by a host of its own creations, trying to map the correct route to follow.

*From Milwaukee Children's Hospital and Department of Pediatrics, Marquette University Medical School.
**Associate Clinical Professor of Pediatrics, Marquette University Medical School.
In the above article Spink concludes, "One of the greatest advancements in medical practice in the last decade has been the introduction of the antibiotics. The impact of these agents upon the course of many infections has been so remarkable that some diseases have been almost eliminated as serious entities." With regard to the phenomenon of bacterial drug resistance he points to old investigations by Paul Ehrlich and he goes on, "As aids in the prevention of chronicity of the infection and of protection against the appearance of resistant parasites, he (Ehrlich) suggested just what we have advocated for the treatment of staphylococcal sepsis, namely, energetic and aggressive treatment with a combination of drugs that had been selected on the basis of sensitivity tests carried out in the laboratory."

William H. Feldman,² on the other hand, formulates some serious doubts as to the wisdom of large-scale use of the various antibiotics. "We are well into an era of promiscuous therapeutics in which the per capita consumption of the newer chemotherapeutic substances is probably second only to aspirin . . . Although these newer medicaments are prescribed with therapeutic intent, they are, like most drugs, potentially poisonous." He
concludes as follows: "The substantial value of modern chemotherapeutic agents is recognized. When used with circumspection, many synthetic and antibiotic agents have life-saving potentialities." (Possibly the understatement of the century!) "However, many of these medicinals, if prescribed unwisely, are definitely hazardous. This is particularly true of agents having a broad antibacterial spectrum and in situations where chemotherapy is continued for prolonged periods of time."

Finland, Maxwell and Weinstein cautiously state, "The fact that harmful effects may follow the use of these drugs should not discourage the physician from applying them when they are definitely indicated."

As to indications for prolonged antibiotic treatment there is at the present time a school that believes firmly in the rational of rheumatic fever prevention by continuous chemotherapy. Hamilton and co-workers state, "A program of continuous prophylaxis to stave off intercurrent streptococcal disease appears thus far to be the best available method for the prevention of recurrent attacks of rheumatic fever." A still more far-going program of streptococcal disease prophylaxis has been advocated by another research team through year-round daily oral administration of 500,000 units of penicillin in rheumatic fever convalescents and the remark is added that there would be no purpose in continuing the practice of closing schools during streptococcal disease epidemics if the entire student body can, simultaneously, be given penicillin orally in the dose and for the period reported.

In a previous publication a Cleveland group suggests that short term intermittent administration of a bactericidal drug, such as penicillin, may

### TABLE II

<table>
<thead>
<tr>
<th>Number of Times Penicillin Therapy Was Administered</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>127</td>
</tr>
<tr>
<td>3</td>
<td>148</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>

500

456

400
be an effective method for the prophylaxis of streptococcal disease and may have certain advantages over the continuous exhibition of suppressive agents such as the sulfonamides."

Elghammer recommends that "the administration of penicillin should be continued into the convalescent period (of rheumatic fever) in order to prevent reinfection. In carriers, penicillin has been found very effective in eradicating streptococci from the oropharynx."

As to an extreme standpoint in the liberal use of antibacterial drugs, the following quotation (Kempe) serves as an example, "Recognition of family infection and treatment of the entire family, including those who are not sick, with the best antibiotics at hand ostensibly offers the best hope for the management and prevention of repeated reinfection from the family source of children who are chronically ill."

To offset this apparent overenthusiasm for wholesale use of antibiotics we may mention two representative articles which in an almost sweeping way deprecate the by now commonly accepted general use of these drugs. An editorial in the New England Journal of Medicine, "Therapeutic Exuberance," approves of the antibiotics only "when the battle is critical or fraught with risk, but neither (as) a substitute for natural resistance and acquired immunity, nor a new invention outmoding the necessity for medical judgment." A still stronger dose of this sort of medical propaganda is contained in an article prepared by the Special Committee on Child Welfare of New York County Medical Society in which it says, "Antibiotics, though invaluable for the treatment of certain inflammatory (?) conditions, have been unduly exploited, overused and abused . . . under no circumstances should a single dose be primarily prescribed. Dosage

**TABLE III**

**Frequency of Administration of Different Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>2892</td>
</tr>
<tr>
<td>Sulfonam.</td>
<td>969</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>555</td>
</tr>
<tr>
<td>Aureomycin</td>
<td>212</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>132</td>
</tr>
<tr>
<td>Terramycin</td>
<td>17</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>17</td>
</tr>
<tr>
<td>Neomycin</td>
<td>5</td>
</tr>
<tr>
<td>Polymyxin B.</td>
<td>1</td>
</tr>
</tbody>
</table>
should be continued until all symptoms and signs of infection have disappeared.” But in the next paragraph we read, “It is conceivable that if the present trend of overdosing with the antibiotics continues, soon physicians may have little or nothing with which to combat the staphylococci.”

Yet what specific conclusions to draw from such generalities of wisdom and warning is another question if we take a look at a different editorial in the Journal of the American Medical Association on “Continued Perils of Pneumonia and Influenza.” Here we read, “The death rate from pneumonia and influenza, which began to decline rapidly after the introduction of the sulfonamides some 15 years ago, has continued its downward trend as the result of widespread use of antibiotics.”

This decline in the death rate, by the way, has been found by Muscato and this author not to be due as much to a lower incidence or any prophylactic effect of the newer drugs, but almost entirely to their curative action. Only in secondary pneumonia, as a complication during the hospital stay of children, a sharp decline almost to the vanishing point became manifest thanks to the liberal use of antimicrobial agents as a hospital routine.

Jawetz and Gunnison in their studies on antibiotic synergism and antagonism have complained that the number of combinations and permutations has become appalling. They have classified these drugs in two groups. Group I. Penicillin, streptomycin, bacitracin, neomycin. Group II. The several tetracyclines and sulfonamides. They consider the agents of Group I frequently synergistic, occasionally indifferent, never antagonistic. The members of Group II neither synergistic nor antagonistic, but simply additive. The addition of Group II to Group I drugs is warranted only if based on laboratory evaluation suggesting synergism.

References as to the presence or absence of such synergism can be found proving or disproving the benefits of any imaginable combination. Here are a few cases in point. Davis found the combination of chloramphenicol and penicillin adequate in pneumococcal pneumonia. Kirby and co-workers found among 10 strains of coliform bacilli isolated from patients with urinary tract infections 43 per cent to be resistant to streptomycin, 29 per cent to chlorotetracycline and oxytetracycline, 2 per cent to chloramphenicol and 3 per cent polymyxin B. Denny and co-workers compared the effects of penicillin, aureomycin, and terramycin on streptococcal infections and concluded that no one drug was consistently more effective than the other two. But they stated that from the standpoint of toxicity penicillin is the drug of choice. It also was more effective than the tetracyclines in short and long term eradication of streptococci from the throat.

Digest of Our Own Repeated Antimicrobial Therapy

Before attempting an interpretation of therapeutic results with repeated administration of antimicrobial drugs obtained in our own cases, it is fitting to present first our clinical material from the statistical point of view. This consisted of all patients who, during the 10 year period from 1944 until about midyear 1954, were admitted to the hospital three or
more times and had undergone during their hospital stay antibiotic or chemotherapy. The total number of cases thus reviewed was 872, while the total number of case histories scrutinized was 3158. In 652 cases there were three admissions with administration of various chemotherapeutical agents, 103 were admitted four times, 72 five times, 37 six times, 21 seven times, 13 eight times, four nine times, three 10 times, three 11 times, one 13 times, 15 times, 16 times and 20 times respectively (Table 1). If we draw an arbitrary line between moderately and exceedingly frequent repetition of chemotherapy, we arrive at the figure of 157 cases who had 6 to 20 admissions for various forms of anti-infectious treatment.

It stands to reason that many of these children will have had more drug therapy for intercurrent diseases given to them as outpatients either at home or otherwise; therefore, the above figures for repeated chemotherapy represent only the minimum actually on record.

In order to characterize the type of clinical material of our survey the important point is that about every morbid condition of childhood prevalent in this general area is represented among these 872 patients. We have laid emphasis before on the absence of any overall policy in selection of cases and of therapy. This increases, in our opinion, the objective value of our clinical material because, in avoiding any preconceived therapeutic program, we are enabled to study what actually has happened to the practice of medicine in these fateful years with regard to childhood infections.

We proceeded to tabulate the pertinent data of each case history as follows:

Name/Dates/Number of admissions/Age on first admission/Age on last admission/Diagnoses on each admission (1-2-3-4-5-6-etc.)/Types of chemotherapy (1-2-3-4-5-6-etc.)/Response (1-2-3-4-5-6-etc.)/Drug allergy.

The ages on first and last admission indicate the period of time over which the repeated drug administration was distributed. This varied, of course, from case to case and as illustration of extremes as far as the time element is concerned we may use the following examples:

A 13 month old girl with meningoccele and urinary tract infection, readmitted for a total of 10 times over a period of 15 months. Surgery was performed on second admission. The following courses of drugs were used: Penicillin nine times, sulfonamides seven times, terramycin once, and chloramphenicol once. The child responded each time favorably and promptly to therapy, and at the age of 28 months she was discharged as recovered. There were no signs of drug allergy or idiosyncrasy.

A one month old premature weighing 3 pounds, 2 ounces, admitted eight times during 11 months with the diagnoses of acute enteritis, pyuria, upper respiratory infection, otitis media, hypoadrenalism, and pneumonia. Drug treatment consisted of penicillin seven times, streptomycin four times, sulfonamides two times. At the age of 12 months the child weighed 17 lbs. and was finally discharged in good health.

A newborn boy was admitted on the first day of life with imperforate anus for emergency surgery. On seven successive admissions several stages of corrective operations were performed. Upon the second admission there was complicating bronchopneumonia. Drug administration consisted of six courses of penicillin, five of streptomycin, five of sulfonamides, two of neomycin, one of chloramphenicol, terramycin, achnomycin, and erythromycin respectively. At the age of two years seven months the child was discharged in good health and free from infections.
In contrast to these cases where repeat chemotherapy has been crowded into a relatively short space of time we may consider the following examples of long range treatment:

A one year nine month old girl was admitted with diagnosis of meningocele and congenital heart disease. Corrective surgery was performed on third and fifth admission. There was a sequence of urinary and respiratory tract infections, 20 hospital admissions all told over a period of more than five years, after which she was discharged in generally satisfactory condition. Chemotherapy consisted of 5 courses of penicillin, seven of sulfonamides, three of streptomycin, seven of aureomycin, two of chloramphenicol and two of terramycin. Sensitivity studies in the last year revealed a previously suspected bacterial resistance to penicillin and aureomycin. Yet, she finally made, after more than five years, a satisfactory recovery on repeated combination antibiotic therapy without untoward allergic side-effects.

A five month old boy was admitted with diagnosis of lobar pneumonia, readmitted as unresolved pneumonia with bronchiectasis. On third admission lobectomy was performed. There was a total of six admissions over a period of eight years and eight months. Drug therapy consisted of five courses of penicillin, two of sulfonamides, one of terramycin. On last admission studies showed complete sensitivity to penicillin. There was no allergic manifestation, and the end result was excellent.

These samplings of our large amount of material do not tell us much about the correctness or the drawbacks of this kind of therapeutic procedure. They do indicate, however, the actual antibiotic "facts of life," free from theoretical inhibitions, as they became established at Milwaukee Children's Hospital following the introduction of these drugs.

As it is physically impossible to report all the 3,158 case histories in detail, we shall proceed in presenting a breakdown of our material which should provide an insight into the overall repeat chemotherapy.

Table II demonstrates the overall frequency of administration of the different drugs, the result of which may be called an antibiotic popularity contest. It shows that penicillin is way out in front with 2,892, followed by sulfonamides 909, streptomycin (given mostly in combination with penicillin) 555, followed by the several tetracycline preparations.

Table III gives the number of times courses of penicillin were repeated. We find that only in 12 cases out of our total other agents were used to the exclusion of penicillin, while in exactly 100 cases five and more courses of penicillin were given.

It is difficult to enumerate or to classify our material from the diagnostic angle because just about the entire range of morbid conditions has been encountered. We already reported one case of prematurity. There were all kinds of congenital malformations, atresias of the intestinal tract or bile duct, heart lesions, cleft palates, clubfoot, microtia, etc. A considerable number of fibrocystic diseases of the pancreas was the object of repeat chemotherapy for obvious reasons. Besides, we find the innumerable varieties of respiratory tract, digestive tract, and urinary tract infections of different severity or even triviality repeatedly admitted and treated antibiotically.

Among the great number of respiratory diseases treated in this group, like acute laryngo-tracheo-bronchitis, lobar and bronchopneumonia, chronic bronchitis and bronchiectasis, we separated 72 cases which were labeled either asthmatic bronchitis or bronchial asthma. The question arose
whether antibiotic substances might have been in any etiological connection with the appearance of asthmatic manifestations or whether the use of these drugs seemed to have any untoward effect.

As it turned out, in 56 of these cases the diagnosis of asthmatic syndromes was made on first or second admission and antibiotic therapy was continued with good results. In 16 the diagnosis of asthma was entered on later admissions; however, in 15 the same medication was continued without ill effect. Only in one, an 11 month old infant, repeated administration of penicillin and streptomycin, while not aggravating the respiratory distress, seemed ineffectual against the underlying infection.

There were 13 who presented skin manifestations resembling allergic dermatitis, like atopic eczema associated with asthma, eczema with secondary infection, etc. This low number of cases may be due to the fact that the presence of an apparently allergic diathesis tended to discourage the use of potentially allergenic agents like molds. Yet in 11 antibiotic therapy was repeated for various reasons in the wake of a subsiding rash without causing exacerbation, while two cases developed assumingly allergic skin eruptions after prolonged and repeated medication (erythema multiforme, roseola) but entirely without any dramatic syndromes. This lack of menacing allergic incidents is in variance with reports about severe reactions following repeated penicillin administration in adults\textsuperscript{17, 18} and we feel justified after scanning our 3158 case histories to stress this absence of severe side effects in childhood.

A more or less separate category was made up of patients admitted for major surgical procedures. There were 168 who underwent either operative procedures like appendectomy, at times following several courses of antibiotic treatment for acute appendicitis or periappendiceal abscess. Others were cases of atresia or stenosis of the intestinal tract and bile duct as previously mentioned, cardiac surgery, pulmonary lobectomy, etc.

However, the largest number of our surgical group, 113, was made up of orthopedic cases, including congenital malformations of the skeleton, postpoliomyelitic deformities for corrective surgery, cases of traumatic surgery, plastic surgery like skin grafting following burns, furthermore cheilo-uranoplastonic operations, otoplastic corrections, and finally 52 tonsillectomies, eight dental extractions with preoperative and postoperative chemotherapy. (These latter 60 not included among the above 168).

It seems remarkable that all the various attending surgeons on our staff, regardless of their specialty, appear to have almost unanimously agreed on including anti-infectious drug therapy in their preoperative and postoperative routine. This could not possibly have been the case, if continuous experience would not have taught them that the advantages of preventing intercurrent infections by far outweighed the occasional episodes of side-reactions. This reviewer, therefore, assumed only the pleasant task of verifying at the hand of the hospital records the practical absence of severe drug idiosyncrasies or allergies.

Another more problematic aspect of simultaneous and successive anti-
microbial therapy is the degree of effectiveness of the different agents, single or in combination, at infrequent or frequent intervals. Here we have to refer back to our statistics of drug administration which reveals that repetitious penicillin administration, in particular, four or more courses in 248 cases) retained its effectiveness in the great majority while the wide spectrum antibiotics (with a total of 485 courses of treatment) were applied either selectively as, for instance, in severe urinary and intestinal tract infections following sulfonamides or in obscure refractory cases of mixed infection where the desired response to the standard drugs, penicillin, sulfonamides, streptomycin, had proved disappointing. We are well aware of the variations in bacterial sensitivity to the whole array of antimicrobial agents and we have also encountered a number of clinically drug resistant infections, and this by the way not only among the staphylococcus group but also among streptococcus hemolyticus (but not viridans), although according to our experience complete therapeutic failures are strikingly fewer in number than the in vitro bacterial resistance studies would indicate. However, we intend to devote a separate study in the near future to this apparent absence of a parallelism between in vivo and in vitro microbial drug sensitivity.

This report on therapeutic results would evidently be incomplete without adding an account of mortality among these 872 cases. There were 39 deaths recorded. The causes were as follows: 10 leukemias, one Hodgkin's disease, one Wilms' tumor, one reticuloendotheliosis, one aplastic anemia, four fibrocystic diseases of the pancreas, four congenital heart lesions, three cases of congenital hydrocephalus, one subdural hematoma, one cerebellar tumor, two imperforate anus, one atresia of the bile duct, one intussusception, two pneumonias, one meningococcic meningitis, one tuberculous meningitis, one nephrosis, one pseudohermaphroditism with adrenal insufficiency, one ulcerative colitis, and one pulmonary moniliasis. In none of these cases, including the longstanding systemic monilia infection and the aplastic anemia, could etiological connection be established between chemotherapy and the fatal outcome. However, the two pneumonia deaths, the meningococcic meningitis, and the ulcerative colitis, while admitted and readmitted in far advanced stages of the disease, must be classified as therapeutic failures.

Discussion

In the perennial struggle between pathogenic microbes and the human race the introduction of the aniline derivatives and of the mold derivatives have tipped the scale decidedly in favor of the human race.

As a desperate counter measure against the deadly molds the pathogenes have attempted a comeback through acquired resistance, possibly on the principle of survival of the fittest.

Yet large scale clinical experience still reveals day after day that a proper task force of antibiotic molds thrown into the battle without delay will route the bacterial enemy invader and save the day for the human host.
Only in rare instances will the molds, fighting on the side of men, turn traitor and cause serious harm to his traditional ally. In children such acts of allergic treachery on the part of the friendly molds occur still more infrequently than in adults.

After the first period of awe and enthusiasm over the antibiotic victories had somewhat dissipated, an attitude of critical assessment of gains and losses set in, and as so often is the case in political as well as in medical history, the pendulum has swung quite far to the other side. Numerous voices are being heard about the antibiotics being "security risks," ineffective, stymying the natural immunological defenses, etc.

That is why a "do it yourself" and "look for yourself" attitude appeared to be the only sure way of arriving at valid conclusions about our past experiences and to formulate a rational therapeutic policy for the future.

SUMMARY

1. In a review of publications on antimicrobial therapy many divergent conclusions as to response to the available drugs are being pointed up. There is no consensus of opinion as to the occurrence and significance of (a) microbial sensitivity and resistance to drugs, (b) synergism, indifference or antagonism of drug combinations, (c) allergic or anaphylactic reactions of the human host.

2. The case histories of 872 patients who had received between three and 20 successive courses of antibiotic or chemotherapy at Milwaukee Children's Hospital within a 10 year period (3158 individual hospital admissions all told) were closely scrutinized and tabulated according to age, number of admissions, diagnoses and complications, type of drug administration, therapeutic response and allergic side effects.

3. The overall frequency of administration of the different drugs, which may be termed an antibiotic popularity contest, shows, as expected, penicillin way out in front with 2,892, followed by sulfonamides 909, streptomycin (given mostly in combination with penicillin) 555, followed by the several tetracycline preparations.

4. Lack of favorable clinical response to chemotherapy was hardly ever encountered although in cases with underlying severe systemic pathology like fibrocystic disease of pancreas, leukemia, congenital malformations, and possibly also agammaglobulinemia, etc., drug treatment could not accomplish more than temporary improvement, at times even after numerous exacerbations.

5. Penicillin, in particular, was administered in as many as 15 courses in one patient, in 248 cases four and more times. The clinical response in practically all cases was entered as partially or entirely favorable. Penicillin-streptomycin combination became a favorite routine in patients before specific bacteriological information was available. Sulfonamides and the tetracyclines were chosen mostly in urinary infections, then whenever bacteriological findings indicated preferential medication and finally in all cases refractory to the more popular drugs; most of these
belonged to the prognostically grave category of leukemias, fibrocystic disease and malformations.

6. In 72 cases of asthmatic bronchitis and bronchial asthma no untoward effects of repeated drug administration were noted. In 13 cases of allergic dermatitis 11 showed clearing in spite of repeated antibiotic therapy, only two developed erythema multiforme and roseola respectively without any threatening syndromes.

7. In 228 cases with major or minor surgery antimicrobial drugs were ordered more or less as a routine preoperative or postoperative procedure. In this policy all the attending members of our surgical staff in the different surgical specialties participated about equally. The results appear to have been most gratifying from the surgical as well as medical point of view.

8. There was a total of 39 fatalities out of 872 cases under review. None of them had even a remote causal connection with drug administration, except possibly two pneumonias in infants, one meningococcic meningitis and one ulcerative colitis, which cases might be classified as therapeutic failures. The rest of them were cases of hopeless prognosis like leukemia, congenital malformations, fibrocystic disease. In most of these cases repeated drug therapy was obviously instrumental in prolonging life.

9. On the basis of this varied and unselected material of hospitalized children it can be stated that the benefits of all the older and newer antimicrobial agents by far outweigh their shortcomings. We, therefore, consider it unwise to overemphasize the comparatively rare therapeutic failures and we do not hesitate to encourage the liberal use of these drugs, whenever indicated, by the younger generation of physicians who have never experienced the utter helplessness (except for immune body therapy) of the preantibiotic and prechemotherapeutic era.

RESUMEN

1. En una revisión de las publicaciones sobre terapia antimicrobiana, se señalan varias conclusiones divergentes en relación a la respuesta a las drogas con que contamos. No hay una igualdad de opinión en lo que se refiere a la frecuencia y significado de (a) sensibilización microbiana y resistencia a las drogas, (b) sinergismo, antagonismo o indiferencia de las combinaciones de drogas y (c) reacción alérgica o anafiláctica en el huésped humano.

2. Las historias de los casos de 872 pacientes que han recibido entre tres y veinte series sucesivas de terapia por antibióticos o de quimioterapia durante un periodo de 10 años (3158 admisiones en total) en el Milwaukee Children’s Hospital fueron escrutinados atentamente y tabulados de acuerdo con su edad, número de admisiones, diagnóstico y complicaciones, tipo de droga administrada, respuesta a la terapéutica y efectos alérgicos colaterales.

3. La frecuencia total de la administración de las diferentes drogas, lo que podíamos llamar un concurso de popularidad de los antibióticos,
muestr ..., como era de esperarse, a la penicilina muy por delante con 2,892,
seguida por las sulfonamidas con 909, estreptomicina (administrada generalmente en combinaciones con penicilina) 555, seguidas por las varias preparaciones de tetraciclina.

4. Casi nunca se encontró falta de respuesta clínica favorable a la quimioterapia a pesar de que en los casos con patología sistémica grave subexistente tales como enfermedad fibroquística del páncreas, leucemia, malformaciones congénitas y también posiblemente agamaglobulinemia, etc. el tratamiento medicamentos no pudo lograr más que mejoría temporal, a veces aún después de numerosas exacerbaciones.

5. La penicilina en particular, fue administrada hasta en 15 series en un paciente y en 248 casos en cuatro o más veces. La respuesta clínica se consideró en todos los casos como parcial o enteramente favorable. La combinación de penicilina-estreptomicina vino a ser la rutina favorita en los pacientes en los cuales no se había obtenido información bacteriológica específica. Las sulfonamidas y las tetraciclinas fueron escogidas en su mayor parte en las infecciones urinarias, después siempre que los hallazgos bacteriológicos las indicaban como medicación preferente y finalmente en los casos refractarios a las drogas más populares, la mayor parte de los cuales pertenecían a la categoría de pronóstico grave como leucemias, enfermedad fibroquística y malformaciones.

6. En 72 casos de bronquitis asmática y de asma bronquial no se notaron efectos dañosos por la administración repetida de drogas. En tres casos de dermatitis alérgica, 11 mostraron limpieza a pesar de la terapia antibiótica repetida, sólo dos desarrollaron eritema múltiple y roseta respectivamente sin ningún síndrome alarmante.

7. En 228 casos con cirugía mayor o menor las drogas antimicrobianas fueron ordenadas más o menos como procedimiento de rutina pre y post-operatorio. Todos los miembros de nuestro grupo quirúrgico de las diferentes especialidades participaron aproximadamente igual de esta política. Los resultados parecen haber sido de lo más halagadores tanto desde el punto de vista quirúrgico como desde el médico.

8. Hubo un total de 39 muertes de nuestro total de 872 casos bajo revisita. Ninguna de ellas tuvo ni la más remota relación causal con la administración de drogas, con la excepción posiblemente de dos neumonías en niños, una meningitis meningocócica y una colitis ulcerativa los cuales se pueden considerar como fracasos de terapéutica. El resto de ellas eran casos de pronóstico desesperado, como leucemia, malformaciones congénitas y enfermedad fibroquística. En la mayor parte de estos casos la terapia repetida con drogas fue obviamente instrumento de la prolongación de su vida.

9. Teniendo como base este material variado y no seleccionado de niños hospitalizados, se puede afirmar que los beneficios de todos los agentes antimicrobianos tanto nuevos como antiguos sobrepasan en mucho a sus limitaciones. Consideramos por lo tanto, poco acertado el acentuar demasiado las fallas terapéuticas relativamente raras y no vacilamos en recomendar el uso liberal de estas drogas, cuando estén indicadas, por la
RESUME

1. En surveillant la littérature sur la thérapie antimicrobienne on constate des conclusions fort divergentes concernant les effets produits par les substances chimiques qui sont à notre disposition. On n’est pas d’accord (a) sur l’occurrence et la valeur de la sensibilité et la résistance microbienne, (b) le synergie, l’indifférence ou l’antagonisme des combinaisons chimiques, (c) les réactions allergiques ou anaphylactiques de l’organisme humain.

2. Les histoires de 872 malades qui ont reçu entre trois et vingt séries de traitements antibiotiques ou chimothérapeutiques à L'Hôpital d'Enfants de Milwaukee au cours de dix ans (3158 admissions en tout) ont été examinées en détail et disposées en forme de tables suivant l’âge, nombre d’admissions, diagnostics et complications, choix de traitement spécifique, effet du traitement, complications allergiques accessoires.

3. En examinant les quels parmi les différents médicaments ont été choisis le plus fréquemment — on pourrait parler de concours de popularité — parmi les antibiotiques — on trouve sans doute la pénicilline fortement en premier place (2892), suivie des sulfanilamides (909), streptomycine, surtout en combinaison avec la pénicilline (555), suivie par plusieurs préparations de tetracycline.

4. L’effet favorable de la chimothérapie, avec très peu d’exceptions, ne faisait jamais doute. Quand même, en cas de maladies graves systémiques comme la fibrocytique du pancréas, la leucémie, les malformations congénitales et possiblement l’agammaglobulinémie, etc., le traitement antimicrobien ne pouvait accomplir qu’une amélioration passante, parfois après des exacerbations nombreuses.

5. En un cas la pénicilline fut donnée autant que 15 fois à un malade, en 248 plus que quatre fois. Dans presque tous le cas l’effet chimique fut recédé comme partiellement ou entièrement favorable. La combinaison pénicilline-streptomycine finissait par être le traitement préféré dans les cas où il n’y avait pas encore d’information spécifique sur la bactériologie. Les sulfanamides et le tetracycline furent choisis particulièrement pour les infections urinaires, et puis aussi quant la détermination bactériologique demandait une médication spécifique, et surtout dans tout les cas où les médicaments plus populaires manquaient de succès, généralement dans les cas de maladies graves comme les leucémies, les affections fibrocytique et les malformations.


7. En 228 cas avec chirurgie majeure ou mineure, les médicaments anti-microbiens étaient prescrits plus ou moins de manière d’une routine pré-

8. Es war 39 Falle unter 872 Fällen in der Klinik. Die einzige, die hatte, Tomycin 2892, war ein Antibiotikum, das nach der Art der Behandlungsperiode hinzugefügt wurde. Die Ergebnisse hatten gezeigt, dass die Beobachtungsphase sehr seltene therapeutische Erfolge waren, aber wir können sicher sein, dass der Einsatz der modernen therapeutischen Methoden nicht nur selten war, sondern wir haben uns nicht entschieden, die Verwendung der freien Unterkleidung von den Substanzen antimikrobiellen, alle Altersgruppen und Modelle, zeigten, dass es mehr Vorteile und Vorteile gegenüber den Vorteilen. Es war jedoch wichtig, dass die Defizite der therapeutischen Maßnahmen unter der Obhut der Kommission für die seltenen Fälle und wir haben die Erfahrung aus dieser Erfahrung nicht genutzt, um die Antibiotikatherapie zu unterstützen, sondern um die therapeutischen Methoden zu verbessern.


ZUSAMMENFASSUNG

1. In einer Literaturübersicht über die antimikrobielle Therapie werden hinsichtlich der Ansprechbarkeit auf die verfügbaren Medikamente viele unterschiedliche Schlussfolgerungen berichtet. Es bestehen Meinungsunterschiede über Vorkommen und Bedeutung von (a) Keimempfindlichkeit und — Resistenz gegenüber den Medikamenten; (b) Synergismus, Indifferenz oder Antagonismus von Arzneimitteln — Kombinationen und (c) allergischen und anaphylaktischen Reaktionen des Menschen.


3. Einen Überblick über die Häufigkeit der Anwendung bereits bekannter antibiotischer Mittel zeigt, wie zu erwarten ist, dass das Penicillin mit 2892 an der Spitze liegt; dann folgen die Sulfonamide mit 909, das Streptomycin mit 555, das meist in Kombination mit Penicillin verabreicht wurde, weiterhin folgen die verschiedenen Tetracyclin-Präparate.

4. Ein Nichtansprechen auf die Chemotherapie wurde fast nie gefunden, es sei denn, dass in Fällen, denen eine schwere Systemerkrankung zu Grunde lag, ferner bei fibrozystischer Erkrankung, bei Leukämien, bei konnatalen Missbildungen, vielleicht auch bei Agammaglobulinämie bei denen, die medikamentöse Behandlung nicht mehr als eine vorüberge-
hende Besserung erzielen konnte, zuweilen sogar nach zahlreichen Exazerbationen.


9. Auf der Basis dieses verschiedenartigen und unausgewählten Krankengutes (Kinder) muss festgestellt werden, dass die Vorzüge der älteren und modernen Chemotherapeutika bei weitem ihre Mängel aufwiegen. Deswegen halten wir es für verkehrt, die relativ seltenen Misserfolge der Chemotherapie zu überwerten und zögern nicht, die freie Anwendung dieser Mittel bei entsprechender Indikation der jüngeren Arztgeneration zu empfehlen, die niemals die äusserste Hilflosigkeit der vor-antibiotischen und vor-chemotherapeutischen Aera, in der nur die Immunkörper-Therapie zur Verfügung stand, erfahren hat.

REFERENCES