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Immunomodulating Effects of Antibiotics: Literature Review

Summary: Antibiotics can interact directly with the immune system. This is a review of the immunomodulating effects of antibiotics. The Medline database on CD-ROM was searched for the years 1987 to 1994 using the following search string: "*thesaurus* explode antibiotics / all AND (*thesaurus* explode immune-system / drug effects OR *thesaurus* immune-tolerance / drug effects)." Aspects of the immune system studied were aspects of phagocyte functions: phagocytosis and killing, and chemotaxis and aspects of lymphocyte functions: lymphocyte proliferation, cytokine production, antibody production, delayed hypersensitivity and natural killer-cell activity. In order to quantify and to compare immunomodulatory properties of antibiotics we calculated an "immune index," defined as:

$$\frac{\text{number of positive statements} - \text{number of negative statements}}{\text{total number of statements.}}$$

Concerning phagocytosis, positive effects were observed for cefodizime, imipenem, cefoxitin, amphotericin B and clindamycin and negative effects for erythromycin, roxithromycin, cefotaxime, tetracycline, ampicillin and gentamicin. Clindamycin, cefoxitin and imipenem induce enhancement of chemotaxis, whereas cefotaxime, rifampicin and teicoplanin decrease chemotaxis. Regarding lymphocyte proliferation, cefodizime has the strongest stimulating effect, whereas tetracycline has the strongest negative effect. Except for erythromycin and amphotericin B the number of statements reported is too small to be conclusive for the interpretation of effects on cytokine production. Erythromycin and amphotericin B appear to stimulate cytokine production. As to antibody production, cefodizime has the strongest positive effect, whereas josamycin, rifampicin and tetracycline have marked negative effects. For delayed hypersensitivity and the natural killer-cell activity the number of statements is too small for any single antibiotic to be conclusive. There are three markedly immuno-enhancing antibiotics (imipenem, cefodizime and clindamycin) and eight markedly immuno-depressing antibiotics (erythromycin, roxithromycin, cefotaxime, tetracycline, rifampicin, gentamicin, teicoplanin and ampicillin).

Introduction

Antibiotics are widely used as bacteriostatic or bactericidal drugs in the therapy of bacterial infections. Besides the respective interactions between antibiotics and bacteria, and between the immune system and bacteria, antibiotics also directly interact with the immune system. This is evidenced by both experimental and clinical research. When a given antibiotic causes immune depression, it may counteract its own bactericidal effect. The impact of antimicrobial drugs on the immune system, already important in the patient with intact immune function, may become even more substantial in patients with immunological disease and/or deficiency.

In 1982, *Hauser* and *Remington* published a comprehensive review on the effect of antibiotics on the immune response [1]. They concluded that a potential for immunosuppression existed for several antibiotics, although the clinical significance of the experimental observations remained to be elucidated; the necessity for an intelligent and restrained prescription of antibiotics was underscored, especially in immunosuppressed patients. In 1989, *Korzeniowski* stated that the majority of studies on the immune effects of antibiotics was performed *in vitro*; only few studies were performed in patients receiving antibiotics, whereas virtually no studies were based on patients at highest risk, i.e. the immunocompromized. He concluded that studies on the immune effects of antibiotics were still in their infancy [2].

The immunomodulating effects of antibiotics are also considered in several other reviews [1–5], but in many cases only limited aspects of immune function or a limited number of antibiotics were considered; in addition, to our knowledge, recent data generated during the last few years, have not been subjected to review.

Materials and Methods

Selection of papers: Studies addressing the influence of antibiotics on the immune system were identified by searching the MEDLINE database on CD-ROM for the years 1987 to 1994 using the

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following search string: "*thesaurus* explode antibiotics / all AND (*thesaurus* explode immune-system / drug effects OR *thesaurus* immune-tolerance / drug effects)."
The reference lists of all the primary studies and review papers were checked to identify any reference not found in the MEDLINE search.
Of all identified papers the following were omitted: papers in any language other than English, papers dealing with indirect influences on the interactions of pathogens, antibiotics, the immune system and the host as a whole (such as the penetration of anti-infective agents into immune cells, the influence of sub-MIC on phagocytosis and intraphagocytic killing, bone marrow suppression and blood dyscrasias and anti-neoplastic antibiotics) and articles where the methodology was insufficiently defined.
Data selection and analysis: Each statement of each paper was evaluated for quality and classified according to the aspect of the immune system studied, to the approach and the model used; then the effect sign (negative, neutral or positive) was determined and an "immune index" calculated.
Aspects of the immune system studied: The interactions between antibiotics and the immune system were classified into several categories.
A) Phagocyte functions considered were phagocytosis and killing, and chemotaxis.
A1) Phagocytosis was defined as the process by which phagocytes ingest foreign material. Killing or bacterial destruction is very closely associated with and directly follows upon phagocytosis and was defined as the process by which phagocytes degrade foreign material. Because many assays measure the combined effect of phagocytosis plus intracellular killing [3], these two aspects were classified together under "phagocytosis."
A2) Chemotaxis was defined as the process by which phagocytes are attracted and migrate to the vicinity of pathogenic microorganisms by a number of factors: bacterial compounds, tissue proteases and complement components.
B) Lymphocyte functions considered were lymphocyte proliferation, cytokine production, antibody production, delayed hypersensitivity and natural killer-cell activity.
B1) Lymphocyte proliferation is the functional capacity of lymphocytes to proliferate following their exposure to antigens or mitogens. It results in intracellular changes and as a subsequent development into lymphoblasts.
B2) Cytokines are hormone-like peptides or glycopeptides that regulate many biological processes (cell growth, cell activation, inflammation, immunity, tissue repair, fibrosis and morphogenesis).
B3) Antibody production is the process whereby plasma cells secrete immunoglobulins.
B4) Delayed hypersensitivity is a cell-mediated immune reaction modulated by specifically sensitized T cells that starts hours or days after contact with the antigen and which consists mainly of mononuclear cell infiltration and tissue induration.
B5) Natural killer-cell activity concerns cytotoxicity rather than phagocytosis. Natural killer cells are specialized in killing tumor cells and virus-infected cells without the need for antibody.
Study approach and model: The approach used to study a given immune effect was classified as being *in vivo*, *ex vivo* or *in vitro*. Simultaneous consideration of the immune status and the presence or absence of infection leaves us with the following four options for the *in vivo* and *ex vivo* approach:
1. no infection nor immunodeficiency: healthy volunteer;
2. immunocompromized patient without infection;
3. infection in a patient without immune impairment;
4. infection in an immunocompromized patient.
The immunocompromized states include uremia, diabetes mellitus, liver cirrhosis, burns, surgery, cancer and antineoplastic chemotherapy.
Effect sign: We defined as "statement" each conclusion of experimental evidence concerning a given antibiotic and a given immune effect. Therefore every selected article has at least one statement; however, most papers contain more than one statement, because they describe several immune effects and/or evaluate several antibiotics at a time.
Each statement was attributed to a positive, neutral or negative sign. When the immune effect was studied for a given antibiotic using two or more different and independent methods (e.g. use of agarose migration and a Boyden chamber for studying chemotaxis), two or more statements were taken into account, and the sign of these statements was independently scored.
When the same immune effect for a given antibiotic was studied using two related methods (e.g. study of lymphocyte proliferation after stimulation with phytohaemagglutinin, concanavalin A or pokeweed mitogen), only one statement was scored. In case of discordant results with related methods and/or at different antibiotic concentrations, only the result of the most reliable method and the concentration which conformed most with the one observed in *in vivo* conditions was retained.
Only statistically significant changes were taken into account.
Immune index: In order to quantify and to compare immunomodulatory properties of antibiotics we calculated an "immune index," defined as:

$$\frac{\text{number of positive statements} - \text{number of negative statements}}{\text{total number of statements}}.$$

Results

In order to summarize all selected statements, we classified them according to the immune function under study. These data are reviewed in Table 1. Table headings consist of immune effect (phagocytosis, chemotaxis, lymphocyte proliferation, cytokine production, antibody production, delayed hypersensitivity and natural killer cell activity) and effect sign (negative, neutral or positive). For each statement represented in the table, the study approach (*in vivo/ex vivo/in vitro*), the model (infection: yes or no, and immunodepression: yes or no), the antibiotic and the reference number are given.
In Table 2 the immunoregulatory profiles of a number of selected antibiotics are presented. Table 2a consists of antibiotics which have at least ten independent statements, whereas Table 2b consists of antibiotics with between three and nine independent statements and an absolute value of the "immune index" of more than 0.70.
For each selected antibiotic the calculated "immune index," the total number of statements and the distribution of this number according to effect sign are given. For each statement the sign of the effect, the immune effect, the study approach (*in vivo/ex vivo/in vitro*), the model (infection: yes or no, and immunodepression: yes or no), and the reference number are given.
For the same antibiotics as in Table 2a, data are further summarized in Table 3, giving the overall "immune index"

Table 1: Overview of all statements classified according to immune effect. Approach: study approach (*in vivo / ex vivo / in vitro*).

PHAGOCYTOSIS				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Azithromycin	8
	NO	NO	Cefminox	9
	YES	NO	Clindamycin	10
	NO	NO	Erythromycin	8
	YES	NO	Netilmicin	10
Ex vivo	NO	NO	Gentamicin	11
	NO	NO	Tetracycline	11
In vitro			Actinomycin D	12
			Amikacin	13
			Amphotericin B	14
			Ampicillin	15, 16, 17
			Azithromycin	8
			Benzythine	18
			Cephapirin	
			Benzathine	18
			Cloxacillin	
			Bifonazole	14, 19
			Carfecillin	13
			Cefoperazone	16
			Cefotaxime	16, 20
	YES	NO	Cefotaxime	21
	NO	YES	Cefotaxime	21
			Ceftazidime	16
			Cefuroxime	22
			Cephacetrile	13
			Cephalothin	23
			Cephapirin	13
			Chloramphenicol	24, 20
			Clindamycin	25, 20
			Courmermycin	26
			Cycloheximide	27
			Cyclopentilrifam-picin	28
			Doxycycline	13
			Erythromycin	25, 29, 30, 31, 8
			Florfenicol	32
			Gentamicin	13
			Itraconazole	14, 19
			Ketoconazole	14
			Miconazole	14
			Minocycline	13
			Nafcillin	33
			Novobiocin	13
			Penicillin	17
			Piperacillin	16
			Pristinamycin	13
			Rifampicin	20
			Rifamycin SV	28
			Roxythromycin	25, 34, 30, 35
			Novobiocin	18
			Sulbactam	15
			Teicoplanin	36, 37, 38
			Tetracycline	39, 20
			Tobramycin	20, 13
			Trimethoprim	25
			Vancomycin	36

PHAGOCYTOSIS				
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Benzathine Cepharin	40
	NO	NO	Cefoperazone	41
	NO	YES	Ceftriaxone	42
	NO	NO	Coumermycin	43
	NO	NO	Daptomycin	43
	NO	NO	Novobiocin	40
	NO	NO	Teicoplanin	43
	NO	NO	Tetracycline	44
	NO	NO	Vancomycin	43
Ex vivo			Azithromycin	45
	NO	NO	Cefodizime	46
	NO	NO	Chloramphenicol	11
	NO	YES	Co-trimoxazole	47
	YES	NO	Erythromycin	48
		YES	Rifampicin	49
In vitro			5-Fluorocytosine	14
			Amikacin	33, 26
			Amoxicillin	13, 50
			Amphotericin B	51, 52, 53
			Ampicillin	13, 20
			Ansamycin	26
			Apramycin	13
			Azithromycin	54
			Bacitracin	13
			Benzylpenicillin	20
			Carbenicillin	13
			Cefaclor	13
			Cefadroxil	13
			Cefalothin	13
			Cefamandole	13
			Cefazolin	33, 13
	YES	NO	Cefazolin	21
	NO	YES	Cefazolin	21
			Cefdinir	55
		NO	Cefodizime	56
		YES	Cefodizime	56
			Cefodizime	57
	NO	NO	Cefodizime	58
			Cefonicid	59
			Cefoperazone	13
			Cefotaxime	13
			Cefoxitin	13
	YES	NO	Cefoxitin	21
	NO	YES	Cefoxitin	21
			Cefpodoxime	60
			Cefsulodin	13
			Ceftazidime	33
	NO	NO	Ceftibuten	61
			Ceftizoxime	13
	NO	NO	Ceftibuten	61
			Ceftizoxime	13
	NO	NO	Ceftizoxime	62
			Ceftriaxone	63, 13
			Cefuroxime	64, 13
			Cephalothin	13
			Cephradine	13
			Chloramphenicol	25, 32
			Cinoxacin	13
			Ciprofloxacin	26, 13
			Clindamycin	22, 65, 26
			Cloxacillin	13
			Co-trimoxazole	33
			Dapsone	66

continued

Table 1 continued

PHAGOCYTOSIS				
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vitro			Doxycycline	67
			Enoxacin	26
			Erythromycin	54, 68, 69, 34, 35, 13
			Florfenicol	24
			Fluconazole	14, 19
			Flumequine	13
			Framycetin	13
			Fusidic acid	70, 13, 20, 71
			Gentamicin	25, 33, 26
			Gramicidin	13
			Hetacillin	13
			Imipenem	72, 73
			Imipenem + Cilastatin	57
			Josamycin	68, 34, 35
			Lincomycin	25
			Mecillinam	13
			Meropenem	72
			Metronidazole	20
			Miconazole	53
			Miokamycin	69
			Miomycine	68
			Moxalactam	13
			Nafcillin	13
			Nalidixic acid	13
			Neomycin	13
			Netilmicin	26
			Norfloxacin	13
			Ofloxacin	20
			Oleandomycin	34, 35
			Oxacillin	26
			Oxolinic acid	13
			Oxytetracycline	13
			Pefloxacin	13
			Penicillin	25, 13, 16
			Pipemedic acid	13
			Piperacillin	33
			Rifampicin	49, 26
			Rifamycin SV	49
			Rifapentine	49
			Roxithromycin	54, 68
			Spectinomycin	13
			Spiramycin	68, 34, 35, 13
			Streptomycin	13
			Sulbactam	74
			Sulfamethoxazole	20
			Teicoplanin	26
			Teramycin	33
			Terbinafine	14
			Tetracycline	44
			Thiamphenicol	24
			Ticarcillin	33
			Tobramycin	33
			Triacetyleandomycin	13
			Trimethoprim	20
			Tylosin tartrate	13
			Vancomycin	37, 33, 26
			Vibunazole	14

PHAGOCYTOSIS				
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Cefbuperazone	75
	NO	NO	Cefodizime	76
	NO	YES	Cefodizime	76, 77, 42
	YES		Clarithromycin	78
	NO		Clarithromycin	78
			Clindamycin	79
	YES	NO	Clindamycin	80
	YES	YES	Clindamycin	81
	NO	NO	Clindamycin	81, 82
	NO	YES	Clindamycin	81
	NO	NO	Imipenem	83
	NO	NO	Imipenem + Cilastatin	83
			Teicoplanin	84
			Vancomycin	84
Ex vivo			Cefodizime	85, 76
	NO	NO	Cefodizime	86, 87
	NO	YES	Cefodizime	88, 89, 58, 47
	YES		Cefpimizole	90
			Ceftazidime	91
	YES	NO	Lincomycin	92
	NO	NO	Miokamycin	93
In vitro			Amphotericin B	94, 95, 96, 33, 52
			Arbekacin	97
			Aztreonam	98, 99, 100, 101
			Cefaclor	102
			Cefamandole	99
			Cefetamet	102
			Cefmetazole	73
			Cefodizime	85, 76, 87, 103, 104
			Cefonicid	105
			Cefoperazone	100
			Cefotaxime	100, 104
	YES	NO	Cefotetan	21
	NO	YES	Cefotetan	21
			Cefotiam	106
			Cefoxitin	107, 73
			Cefpimizole	90, 103
			Cefpirome	64
			Ceftazidime	100
			Ceftizoxim	106
			Chloramphenicol	17
			Cilofungin	52
			Clarithromycin	108
			Clindamycin	81, 79
			Clofazimin	66
			Dirithromycin	109
			Erythromycin	108, 110
			Gramicidin	111
			Imipenem	83, 112, 113
			Imipenem + Cilastatin	83
			Miokamycin	114
			Rifampicin	66
			Roxithromycin	31
			Sulbactam	115
			Teicoplanin	84
			Terbinafine	19
			Vancomycin	84

continued

Table 1 continued

CHEMOTAXIS				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo			Erythromycin	116
	YES	NO	Erythromycin	48
Ex vivo		YES	Rifampicin	49
In vitro			Actinomycin D	12
			Amphotericin B	52, 53
			Ampicillin	117
			Ansamycin	118
			Aztreonam	117
			Cefaclor	102
			Cefadroxil	117
			Cefazolin	117
			Cefetamet	102
		NO	Cefodizime	56
			Cefotaxime	117
	YES	NO	Cefotaxime	21
	NO	YES	Cefotaxime	21
			Cefoxitin	119
			Ceftazidime	117
			Cefuroxime	117
			Cephalothin	117
			Cephapirin	117
			Cephradine	117
			Clindamycin	22
			Cloxacillin	117
			Daptomycin	120
			Doxycycline	121, 122
			Erythromycin	29, 110
			Gramicidin	111
			Griseofulvin	123
			Josamycin	124
			Methicillin	117
			Miconazole	53
			Minocycline	125
			Nafcillin	117
			Neomycin	126
			Netilmicin	120
			Oxacillin	117
			Penicillin	117
			Phenoxymethyl-penicillin	121
			Piperacillin	117
			Rifampicin	118, 49
			Rifampicin	28
			Rifamycin SV	28, 49
			Rifapentine	49
			Rokitamycin	127
			Roxithromycin	34, 35
			Teicoplanin	37, 38
			Terfenadine	128
			Tetracycline	129
			Ticarcillin	117

CHEMOTAXIS				
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Cefoperazone	41
	NO		Clarithromycin	78
	YES	NO	Clindamycin	10
	YES	NO	Netilmicin	10
	NO	NO	Rokitamycin	127
	NO	NO	Tetracycline	44
Ex vivo	NO	NO	Cefodizime	86
	NO	YES	Cefodizime	89
In vitro			6-amino-penicillanic acid	117
			Amikacin	120, 119
			Aminobenzyl penicillin	125
			Ampicillin	130
			Aztreonam	98
			Benzylpenicillin	126, 130
	YES	NO	Cefazolin	21
	NO	YES	Cefazolin	21
		NO	Cefodizime	56
		YES	Cefodizime	56
			Cefoperazone	117
			Cefotaxime	130
			Cefoxitin	117
	YES	NO	Cefoxitin	21
	NO	YES	Cefoxitin	21
			Cefpodoxime	60
			Ceftazidime	119
	NO	NO	Ceftibuten	61
	NO	NO	Ceftizoxime	62
			Ceftriaxone	63, 117
			Cefuroxime	22
			Cephalosporin C	117
			Chloramphenicol	130
			Ciprofloxacin	120
			Clindamycin	120, 130
			Co-trimoxazole	126
			Cyclopentyl-rifampicin	28
			Doxycycline	129
			Enoxacin	120
			Erythromycin	69, 131, 35, 31, 132
			Fleroxacin	120
			Fusidic acid	70, 130
			Gentamicin	120
			Josamycin	131, 35
			Ketoconazole	123
			Latamoxef	119
			Metronidazole	130
			Miokamycin	69, 131
			Ofloxacin	130, 120
			Oleandomycin	35
			Pefloxacin	120
			Rifampicin	130
			Rokitamycin	131
			Roxithromycin	131, 31
			Sisomycin	119
			Spiramycin	35
			Sulbactam	115
			Sulfamethoxazole	130
			Teicoplanin	120
			Tetracycline	44, 130
			Tobramycin	119, 130
			Trimethoprim	130
			Vancomycin	37, 120

and specified "immune indices" for each immune function separately.

Considering these tables, there are three markedly immuno-enhancing antibiotics (imipenem, cefodizime, and clindamycin) and eight markedly immunodepressing antibiotics (erythromycin, roxithromycin, cefotaxime, tetracycline, rifampicin, gentamicin, teicoplanin and ampicillin). There is a higher number of antibiotics with a neutral or even marked negative effect than with a positive effect.

continued

Table 1 continued

CHEMOTAXIS				
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo		YES	Aztreonam	133
			Chloramphenicol	134
	YES	YES	Clindamycin	81
	NO	NO	Clindamycin	81, 135
	NO	YES	Clindamycin	81
	NO	NO	Imipenem	83
	NO	NO	Imipenem + cilastatin	83
Ex vivo	NO	YES	Cefodizime	86
			Erythromycin	131
			Josamycin	131
	YES	NO	Lincomycin	92
			Miokamycin	131
			Roxithromycin	131
In vitro			2-acetyl erythromycin	121
			Amoxicillin	124
			Amphotericin B	53
			Cefmetazole	136, 73
		YES	Cefodizime	56
	YES	NO	Cefotetan	21
	NO	YES	Cefotetan	21
			Cefotiam	125
			Cefoxitin	107, 136, 73
			Cefsulodin	117
			Cephaloridine	117
			Cilofungin	52
			Clindamycin	81
			Erythromycin	30, 121
			Imipenem	136, 83, 112, 73
			Imipenem + cilastatin	83
			Josamycin	34
			Miconazole	53
			Oxacillin	120
			Roxithromycin	30

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An overall immunomodulating effect in a given direction does not necessarily mean that the signs are the same for each of the individual specific immune functions under study.

For many antibiotics, the specific "immune indices" are not available for several immune effects, because no studies have been performed. It should be stressed that Table 3 is restricted to antibiotics that have been studied most intensively. For the remaining, less reported antibiotics, even more study results are missing.

Of all 670 statements reported, 309 are related to phagocytosis and killing, 176 to chemotaxis, 70 to lymphocyte proliferation, 54 to cytokine production, 39 to antibody production, 13 to delayed hypersensitivity and nine to natural killer-cell activity.

Of the 670 statements reported, 517 were based on *in vitro* data, 38 on *ex vivo* data and 115 on studies performed *in vivo*.

The immune index of the 128 statements related to models evaluating immunocompetent subjects is +0.08, whereas the immune index of the 32 statements related to models evaluating immunodepressed subjects is +0.50.

Of all 670 statements, 30 concern models with infection.

Of all 670 statements, 24 concern models without infection but with immune impairment. Of these 24, 15 show a positive effect, as opposed to seven showing a neutral effect and only two showing a negative effect.

Of a total number of 153 antibiotics submitted for evaluation, only 16 could be found with ten reported statements or more.

Discussion

Antibiotics play a key role in the treatment of bacterial and fungal infections and are among the most frequently prescribed drugs. It is conceivable that at least some antibiotics may interact with the immune system, but this possibility is frequently not taken into account. In addition, reviews on possible interactions between antibiotics and the immune function are scant [1–5] and do not contain new information generated in the last years.

Overall Effect on Immune Function

In agreement with *Korzeniowski* [2] and *Milatovic* [6], we found a marked heterogeneity in the models and techniques used for estimating the degree of immunomodulation. This makes conclusive interpretation sometimes difficult. Nonetheless, we have found that certain antibiotics have a potent immunomodulating capacity compared to others.

Overall, imipenem, cefodizime and clindamycin have been shown in several studies using different models to have a marked immunostimulating effect, while the number of statements is sufficient to confirm the evidence.

In contrast, erythromycin, roxithromycin, cefotaxime, tetracycline, rifampicin, gentamicin, teicoplanin and ampicillin are suggested to have a marked immunodepressing effect.

Specific Aspects of Immune Function

Concerning phagocytosis, cefodizime, imipenem, cefoxitin, amphotericin B and clindamycin have positive effects; erythromycin, roxithromycin, cefotaxime, tetracycline, ampicillin and gentamicin have negative effects.

Clindamycin, cefoxitin and imipenem induce enhancement of chemotaxis, whereas cefotaxime, rifampicin and teicoplanin decrease chemotaxis. Note the virtual lack of effect for cefodizime, in contrast to most other functions under evaluation.

Concerning lymphocyte proliferation, cefodizime has the strongest stimulating effect, whereas tetracycline has the strongest negative effect.

Except for erythromycin and amphotericin B the number of statements reported is too small to be conclusive for interpretation of effects on cytokine production. Erythromycin and amphotericin B appear to stimulate cytokine production.

Concerning antibody production, cefodizime has the strongest positive effect, whereas josamycin, rifampicin

Table 1 continued

LYMPHOCYTE PROLIFERATION				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Cefotaxime	137
	NO	NO	Ketoconazol	23
In vitro			Amikacin	138
			Amoxicillin	23
			Amphotericin B	139
			Aztreonam	23
			Bafilomycin	140
			Cefamandole	23
			Cefotaxime	23
			Cefoxitin	141
			Ceftazidime	23
			Cephalothin	23, 141
			Chloramphenicol	142
			Ciprofloxacin	23
			Clarithromycin	143
			Clindamycin	23
			Cloxacillin	23
			Erythromycin	29, 144
			Fosfomycin	145
			Gentamicin	138, 23
			Imipenem	23
			Kanamycin	138
			Ketoconazole	23
			Metronidazole	23
			Minocycline	146, 147, 148
			Penicillin	23
			Rifampicin	23
	NO	NO	Rosoxacin	149
			Roxithromycin	150
			Tetracycline	23, 148, 151, 138
			Ticarcillin	23
			Vancomycin	23
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Ampicillin	152
	NO	NO	Cefodizime	137
	NO	NO	Cephalothin	23
	YES	NO	Ciprofloxacin	153
	NO	NO	Ciprofloxacin	23
	YES	NO	Ofloxacin	154
	NO	NO	Rifampicin	23
	NO	NO	Sulbactam-ampicillin	152
In vitro	NO	NO	Amifloxacin	149
			Benzylpenicillin	138
	NO	NO	Ciprofloxacin	149
	NO	NO	Norfloxacin	149
			Penicillin	141
			Sulfadiazine	155
			Tetroxoprim	155
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	YES	NO	Cefodizime	156
	NO	NO	Cefodizime	157
	NO	YES	Cefodizime	158
	NO	NO	Cefotaxime	157
	NO	NO	Tiprotimod	157
Ex vivo	NO	NO	Cefodizime	46, 86
	NO	YES	Cefodizime	159
In vitro			Azithromycin	160
			Cefmetazole	161
			Cefodizime	159
			Imipenem	161, 162
			Amphotericin B	163
			Roxithromycin	164

CYTOKINE PRODUCTION				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Gentamicin	165
	NO	NO	Liquamycine	165
			Polymyxin B	166
			Roxithromycin	167
In vitro			Amphotericin B	168
			Ciprofloxacin	169
			Clarithromycin	143
			Fusidic acid	170
			Minocycline	147
			Pefloxacin	169
			Polymyxin B	166
			Roxithromycin	164, 167
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Ampicillin	152
	YES	NO	Ofloxacin	154
	NO	NO	Sulbactam-ampicillin	152
In vitro			Cefaclor	171
			Cefadroxil	171
			Ciprofloxacin	171
			Doxycycline	171
			Erythromycin	171
			Ofloxacin	171
			Pefloxacin	171
			Penicillin	171
			Spiramycin	171
			Sulfadiazine	155
			Tetracycline	146
			Tetroxoprim	155
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo			Amphotericin B	172
	NO	NO	Erythromycin	173, 174
			Roxithromycin	175
In vitro			Amphotericin B	176
			Arbekacin	97
			Azithromycin	160
			Cefamandole	177
			Cefoxitin	141
			Ceftazidime	177
			Cephalexin	177
			Cephalothin	141
			Ciprofloxacin	178
			Clindamycin	177
			Erythromycin	179
			Gentamicin	166
			Lincomycin	177
			Minocycline	146
			Penicillin	141
			Piperacillin	178
			Polymyxin B	180
			Roxithromycin	164, 179
			Spiramycin	179
			Sulbactam-ampicillin	177
			Teicoplanin	177

continued

Table 1 continued

ANTIBODY PRODUCTION				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	YES	NO	Cefonicid	181
	NO	NO	Cefotaxime	137
	NO	NO	Josamycin	182
	NO	NO	Liquamycin	165
In vitro			Cephalothin	142
			Fosfomycin	145
			Josamycin	182
			Polymyxin B	142
			Rifampicin	142
			Tetracycline	142
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Ampicillin	152
	NO	NO	Cefmetazole	183
	NO	NO	Cefodizime	137, 57
	NO	NO	Cefotaxime	183
	NO	NO	Cefotiam	183
	NO	NO	Cefoxitin	183
	NO	NO	Cephalothin	23
	NO	NO	Ciprofloxacin	23
	NO	NO	Gentamicin	165
	NO	NO	Imipenem + cilastatin	57
	NO	NO	Ketoconazol	23
	YES	NO	Ofloxacin	154
	NO	NO	Rifampicin	23
	NO	NO	Sulbactam-ampicillin	152
	NO	NO	Tetracycline	23, 184
In vitro			Azithromycin	160
			Erythromycin	185
			Josamycin	185
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo			Arbekacin	97
	NO	NO	Cefodizime	157
	NO	NO	Cefoperazone	183
	NO	NO	Cefotaxime	157
	NO	NO	Ceftezole	183
	NO	NO	Clindamycin	184
	NO	NO	Tiprotimod	157
Ex vivo	NO	NO	Cefodizime	85
	NO	YES	Cefodizime	85

DELAYED HYPERSENSITIVITY				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Cefotaxime	137
	NO	NO	Gentamicin	165
	NO	NO	Liquamycine	165
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Cefodizime	137, 57
	NO	NO	Coumermycin	43
	NO	NO	Daptomycin	43
	NO	NO	Imipenem + cilastatin	57
	NO	NO	Teicoplanin	43
	NO	NO	Vancomycin	43
In vitro			Clarithromycin	108
			Erythromycin	108
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo			Clindamycin	79

NK CELL ACTIVITY				
NEGATIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO	NO	Gentamicin	165
	NO	NO	Liquamycine	165
In vitro			Cefodizime	186
			Nitrofurantoin	142
NEUTRAL EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	YES	NO	Amoxicillin	187
	NO	NO	Miokamycin	93
POSITIVE EFFECT				
APPROACH	INF	ID	ANTIBIOTIC	REF
In vivo	NO		Clarithromycin	78
Ex vivo	YES	NO	Lincomycin	92
	YES	NO	Miokamycin	187

INF: infection (no: model without infection; yes: model with infection; blanco: model not specified); ID: immunodeficiency (no: immunocompetent model; yes: immunodepressed model; blanco: model not specified; REF: reference number.

and tetracycline have marked negative effects.

For delayed hypersensitivity and natural killer-cell activity the number of statements is too small for any single antibiotic to be conclusive.

Of the total number of 670 statements reported, 72% are related either to phagocytosis and killing (309) or to chemotaxis (176). An intermediary number of reports is related to lymphocyte proliferation (70), cytokine production (54) and antibody production (39). Little information concerns delayed hypersensitivity (13) or natural killer-cell activity (9).

Subsequently, our knowledge about the potential immunomodulating capacity of antibiotics is mainly related to two specific functions of the total immune system. Nevertheless it should be stressed that the phagocytic process and the subsequent killing of microorganisms can be considered as the endpoint of the immune response to bacterial and fungal invasion.

In Vivo versus in Vitro Approach

Of all statements reported, 517 were based on *in vitro* data, 38 on *ex vivo* data and only 115 on studies performed *in vivo*. We can assume that *in vivo* and possibly also *ex vivo* methods will be most representative for the clinical condition. Therefore, as already stated by *Labro* and *El Benna* [5], *Korzeniowski* [2], *Hauser* and *Remington* [1] and *Gemmell* [4], the clinical relevance of *in vitro* studies, which compose the vast majority of the published data, still may remain a matter of debate.

Study Models

It is remarkable that only a minority of studies have been undertaken on primary conditions of immune depression, such as diabetes mellitus, liver cirrhosis, cancer, and uremia. The immune index of the 128 statements related to

Table 2a: Immunoregulatory profiles for antibiotics with at least ten statements.

+ 0.24 Amphotericin B

17*	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
5#	NEGATIVE	Chemotaxis	*In vitro*			52, 53
		Cytokine prod.	*In vitro*			168
		Lymphoc. prolif.	*In vitro*			139
		Phagocytosis	*In vitro*			14
3#	NEUTRAL	Phagocytosis	*In vitro*			51, 52, 53
9#	POSITIVE	Chemotaxis	*In vitro*			53
		Cytokine prod.	*In vitro*			172
			In vitro			176
		Lymphoc. prolif.	*In vitro*			163
		Phagocytosis	*In vitro*			94, 95, 96, 33, 52

– 0.40 Ampicillin

10	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
4	NEGATIVE	Chemotaxis	*In vitro*			117
		Phagocytosis	*In vitro*			15, 16, 17
6	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	152
		Chemotaxis	*In vitro*			130
		Cytokine prod.	*In vivo*	NO	NO	152
		Lymphoc. prolif.	*In vivo*	NO	NO	152
		Phagocytosis	*In vitro*			13, 20

+ 0.60 Cefodizime

45	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
2	NEGATIVE	Chemotaxis	*In vitro*		NO	56
		NK cell activity	*In vitro*			186
14	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	137, 57
		Chemotaxis	*Ex vivo*	NO	NO	86
				NO	YES	89
			In vitro		NO	56
					YES	56
		Delayed hypersens.	*In vivo*	NO	NO	137, 57
		Lymphoc. prolif.	*In vivo*	NO	NO	137
		Phagocytosis	*Ex vivo*	NO	NO	46
			In vitro		NO	56
					YES	56
						57
				NO	NO	58
29	POSITIVE	Antibody prod.	*In vivo*	NO	NO	157
			Ex vivo	NO	NO	85
				NO	YES	85
		Chemotaxis	*Ex vivo*	NO	YES	86
			In vitro		YES	56
		Lymphoc. prolif.	*In vivo*	YES	NO	156
				NO	NO	157
				NO	YES	158
			Ex vivo	NO	NO	46, 86
			Ex vivo	NO	YES	159
			In vitro			159
		Phagocytosis	*In vivo*	NO	NO	76
				NO	YES	76, 77, 42
			Ex vivo			85, 76
				NO	NO	86, 87
				NO	YES	88, 89, 58, 47
			In vitro			85, 76, 87, 103, 104

– 0.42 Cefotaxime

19	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
12	NEGATIVE	Antibody prod.	*In vivo*	NO	NO	137
		Chemotaxis	*In vitro*			117, 119
				YES	NO	21
				NO	YES	21
		Delayed hypersens.	*In vivo*	NO	NO	137
		Lymphoc. prolif.	*In vivo*	NO	NO	137
			In vitro			23
		Phagocytosis	*In vitro*			16, 20
				YES	NO	21
				NO	YES	21
3	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	183
		Chemotaxis	*In vitro*			130
		Phagocytosis	*In vitro*			13
4	POSITIVE	Antibody prod.	*In vivo*	NO	NO	157
		Lymphoc. prolif.	*In vivo*	NO	NO	157
		Phagocytosis	*In vitro*			100, 104

+ 0.27 Cefoxitin

15	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
2	NEGATIVE	Chemotaxis	*In vitro*			119
		Lymphoc. prolif.	*In vitro*			141
7	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	183
		Chemotaxis	*In vitro*			117
				YES	NO	21
				NO	YES	21
		Phagocytosis	*In vitro*			13
				YES	NO	21
				NO	YES	21
6	POSITIVE	Chemotaxis	*In vitro*			107, 136, 73
		Cytokine prod.	*In vitro*			141
		Phagocytosis	*In vitro*			107, 73

– 0.09 Ciprofloxacin

11	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
2	NEGATIVE	Cytokine prod.	*In vitro*			169
		Lymphoc. prolif.	*In vitro*			23
8	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	23
		Chemotaxis	*In vitro*			120
		Cytokine prod.	*In vitro*			171
		Lymphoc. prolif.	*In vivo*	YES	NO	153
				NO	NO	23
			In vitro	NO	NO	149
		Phagocytosis	*In vitro*			26, 13
1	POSITIVE	Cytokine prod.	*In vitro*			178

+ 0.41 Clindamycin

27	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
5	NEGATIVE	Chemotaxis	*In vitro*			22
		Lymphoc. prolif.	*In vitro*			23
		Phagocytosis	*In vivo*	YES	NO	10
		Phagocytosis	*In vitro*			25, 20
6	NEUTRAL	Chemotaxis	*In vivo*	YES	NO	10
			In vitro			120, 130
		Phagocytosis	*In vitro*			22, 65, 26
16	POSITIVE	Antibody prod.	*In vivo*	NO	NO	184
		Chemotaxis	*In vivo*	YES	YES	81
				NO	NO	81, 135
				NO	YES	81
			In vitro			81
		Cytokine prod.	*In vitro*			177
		Delayed hypersens.	*In vivo*			79
		Phagocytosis	*In vivo*			79
				YES	NO	80
				YES	YES	81
				NO	NO	81, 82
				NO	YES	81
			In vitro			81, 79

continued

* the number preceding each antibiotic is the "immune index" = number of positive statements – number of negative statements/total number of statements
# the numbers in the left column are the total number and the numbers of statements per effect sign. Same abbreviations as in Table 1.

Table 2a continued

– 0.11 Erythromycin

35	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
12	NEGATIVE	Chemotaxis	*In vivo*			116
				YES	NO	48
			In vitro			29, 110
		Lymphoc. prolif.	*In vitro*			29, 144
		Phagocytosis	*In vivo*	NO	NO	8
			In vitro			25, 29, 30, 31, 8
15	NEUTRAL	Antibody prod.	*In vitro*			185
		Chemotaxis	*In vitro*			69, 131, 35,
						31, 132
		Cytokine prod.	*In vitro*			171
		Delayed hypersens.	*In vitro*			108
		Phagocytosis	*Ex vivo*	YES	NO	48
			In vitro			54, 68, 69, 34
						35, 13
8	POSITIVE	Chemotaxis	*Ex vivo*			131
			In vitro			30, 121
		Cytokine prod.	*In vivo*	NO	NO	173, 174
			In vitro			179
		Phagocytosis	*In vitro*			108, 110

– 0.46 Gentamicin

13	EFFECT SIGN	Effect	APPROACH	INF	ID	REF
7	NEGATIVE	Cytokine prod.	*In vivo*	NO	NO	165
		Delayed hypersens.	*In vivo*	NO	NO	165
		Lymphoc. prolif.	*In vitro*			138, 23
		NK cell activity	*In vivo*	NO	NO	165
		Phagocytosis	*Ex vivo*	NO	NO	11
			In vitro			13
5	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	165
		Chemotaxis	*In vitro*			120
		Phagocytosis	*In vitro*			25, 33, 26
1	POSITIVE	Cytokine prod.	*In vitro*			166

+ 0.71 Imipenem

14	EFFECT SIGN	Effect	APPROACH	INF	ID	REF
1	NEGATIVE	Lymphoc. prolif.	*In vitro*			23
2	NEUTRAL	Phagocytosis	*In vitro*			72, 73
11	POSITIVE	Chemotaxis	*In vivo*	NO	NO	83
			In vitro			136, 83, 112, 73
		Lymphoc. prolif.	*In vitro*			161, 162
		Phagocytosis	*In vivo*	NO	NO	83
			In vitro			83, 112, 113

– 0.09 Josamycin

11	EFFECT SIGN	Effect	APPROACH	INF	ID	REF
3	NEGATIVE	Antibody prod.	*In vivo*	NO	NO	182
			In vitro			182
		Chemotaxis	*In vitro*			124
6	NEUTRAL	Antibody prod.	*In vitro*			185
		Chemotaxis	*In vitro*			131, 35
		Phagocytosis	*In vitro*			68, 34, 35
2	POSITIVE	Chemotaxis	*Ex vivo*			131
			In vitro			34

– 0.38 Rifampicin

13	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
6	NEGATIVE	Antibody prod.	*In vitro*			142
		Chemotaxis	*Ex vivo*		YES	49
			In vitro			118, 49
		Lymphoc. prolif.	*In vitro*			23
		Phagocytosis	*In vitro*			20
6	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	23
		Chemotaxis	*In vitro*			130
		Lymphoc. prolif.	*In vivo*	NO	NO	23
		Phagocytosis	*Ex vivo*		YES	49
			In vitro			49, 26
1	POSITIVE	Phagocytosis	*In vitro*			66

– 0.14 Roxithromycin

21	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
10	NEGATIVE	Chemotaxis	*In vitro*			34, 35
		Cytokine prod.	*In vivo*			167
			In vitro			164, 167
		Lymphoc. prolif.	*In vitro*			150
		Phagocytosis	*In vitro*			25, 34, 30, 35
4	NEUTRAL	Chemotaxis	*In vitro*			131, 31
		Phagocytosis	*In vitro*			54, 68
7		Chemotaxis	*Ex vivo*			131
			In vitro			30
		Cytokine prod.	*In vivo*			175
			In vitro			164, 179
		Lymphoc. prolif.	*In vitro*			164
		Phagocytosis	*In vitro*			31

– 0.17 Teicoplanin

12	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
5	NEGATIVE	Chemotaxis	*In vitro*			37, 38
		Phagocytosis	*In vitro*			36, 37, 38
4	NEUTRAL	Chemotaxis	*In vitro*			120
		Delayed hypersens.	*In vivo*	NO	NO	43
		Phagocytosis	*In vivo*	NO	NO	43
			In vitro			26
3	POSITIVE	Cytokine prod.	*In vitro*			177
		Phagocytosis	*In vivo*			84
			In vitro			84

– 0.53 Tetracycline

17	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
9	NEGATIVE	Antibody prod.	*In vitro*			142
		Chemotaxis	*In vitro*			129
		Lymphoc. prolif.	*In vitro*			23, 148, 151, 138
		Phagocytosis	*Ex vivo*	NO	NO	11
			In vitro			39, 20
8	NEGATIVE	Antibody prod.	*In vivo*	NO	NO	23, 184
		Chemotaxis	*In vivo*	NO	NO	44
			In vitro			44, 130
		Cytokine prod.	*In vitro*			146
		Phagocytosis	*In vivo*	NO	NO	44
			In vitro			44

= 0.00 Vancomycin

11	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
2	NEGATIVE	Lymphoc. prolif.	*In vitro*			23
		Phagocytosis	*In vitro*			36
7	NEUTRAL	Chemotaxis	*In vitro*			37, 120
		Delayed hypersens.	*In vivo*	NO	NO	43
		Phagocytosis	*In vivo*	NO	NO	43
			In vitro			37, 33, 26
2	POSITIVE	Phagocytosis	*In vivo*			84
			In vitro			84

* the number preceding each antibiotic is the "immune index" = number of positive statements – number of negative statements/total number of statements
# the numbers in the left column are the total number and the numbers of statements per effect sign. Same abbreviations as in Table 1.

Table 2b: Immunoregulatory profiles for antibiotics with between three and nine statements and an absolute value of the "immune index" greater than 0.70.

+ 1.00 Arbekacin						
4#	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
4#	POSITIVE	Antibody prod.	*In vivo*			97
		Cytokine prod.	*In vitro*			97
		Phagocytosis	*In vitro*			97, 97
+ 0.80 Cefmetazole						
5	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
1	NEUTRAL	Antibody prod.	*In vivo*	NO	NO	183
4	POSITIVE	Chemotaxis	*In vitro*			136, 73
		Lymphoc. prolif.	*In vitro*			161
		Phagocytosis	*In vitro*			73
+ 1.00 Cefotetan						
4	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
4	POSITIVE	Chemotaxis	*In vitro*	YES	NO	21
			In vitro	NO	YES	21
		Phagocytosis	*In vitro*	YES	NO	21
			In vitro	NO	YES	21
+ 1.00 Cefpimizole						
3	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
3	POSITIVE	Phagocytosis	*Ex vivo*	YES		90
			In vitro			90, 103
+ 0.80 Lincomycin						
5	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
1	NEUTRAL	Phagocytosis	*In vitro*			25
4	POSITIVE	Chemotaxis	*Ex vivo*	YES	NO	92
		Cytokine prod.	*In vitro*			177
		NK cell activity	*Ex vivo*	YES	NO	92
		Phagocytosis	*Ex vivo*	YES	NO	92
– 1.00 Liquamycine						
4	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
4	NEGATIVE	Antibody prod.	*In vivo*	NO	NO	165
		Cytokine prod.	*In vivo*	NO	NO	165
		Delayed hypersens.	*In vivo*	NO	NO	165
		NK cell activity	*In vivo*	NO	NO	165
– 0.71 Minocycline						
7	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
6	NEGATIVE	Chemotaxis	*In vitro*			125
		Cytokine prod.	*In vitro*			147
		Lymphoc. prolif.	*In vitro*			146, 147, 148
		Phagocytosis	*In vitro*			13
1	POSITIVE	Cytokine prod.	*In vitro*			146
– 0.75 Rifamycin SV						
4	EFFECT SIGN	EFFECT	APPROACH	INF	ID	REF
3	NEGATIVE	Chemotaxis	*In vitro*			28, 49
		Phagocytosis	*In vitro*			28
1	NEUTRAL	Phagocytosis	*In vitro*			49

* the number preceding each antibiotic is the "immune index" = number of positive statements – number of negative statements/total number of statements

the numbers in the left column are the total number and the numbers of statements per effect sign. Same abbreviations as in Table 1.

models evaluating immunocompetent subjects is +0.08, whereas the immune index of the 32 statements related to models evaluating immunodepressed subjects is markedly higher and reaches a value of +0.50. It is conceivable that there is a lower probability to demonstrate improvement of immune function in immunocompetent models; hence, a positive immunomodulating effect can probably at best be observed in an immunodeficient situation [4].

Of all statements, only 30 concern models with infection. These could represent a less suitable clinical model, as subsequent changes in the immune function could be the consequence of an intrinsic effect of the antibiotic per se but also of the mere disappearance of the infection. The interpretative bias induced by the unpredictable influence of infection on this intrinsic immunologic effect, which, in addition, remains of variable duration, might methodologically only be overcome by the development of comparative studies with very large patient numbers.

Of all statements, only 24 concern models without infection but with immune impairment. Of these, 15 show a positive effect, as opposed to seven showing a neutral effect and only two showing a negative effect. These models can be expected to provide the advantage of 1) an easier composition of homogeneous groups, 2) a smaller variation on baseline and 3) no interference with infection. As a consequence, there is a good chance of demonstrating enhancement of host defence and to allow a clear interpretation of results with reasonably sized patient groups.

Number of Statements

Of a total number of 153 antibiotics submitted to evaluation, only 16 could be found with ten reported statements or more. Among these are several representatives of the most currently used antibiotics, especially for the treatment of sepsis, such as the penicillins, cephalosporins, aminoglycosides, quinolones, macrolides and glycopeptides. It should be emphasized that only a few statements could be found on chloramphenicol and co-trimoxazole. One of the reasons may be that these are older antibiotics that were mainly submitted to evaluation several years ago. In the present survey, we have restricted our evaluation to papers published between 1987 and 1994, so that older studies have not been included. For these earlier data we refer to the excellent review by *Hauser* and *Remington*, published in 1982 [1]. Finally, it is conceivable that recently developed antibiotics have not been included in our tables, as not enough statements could be found as yet.

Conclusion

It is concluded that data on the immunomodulating effects of antibiotics remain heterogeneous, contradictory and for many drugs insufficient. For the adequate prescription of antibiotics, however, their immunomodulating profile should be considered, in the same way as is already the case for the pharmacokinetic profile and the antimicrobial spectrum [7].

Table 3: "Immune index" and number of statements tabulated by immune effect and antibiotic.

	All effects		Phagocytosis		Chemotaxis		Lymphocyte proliferation		Cytokine production		Antibody production		Delayed hypersensitivity		Natural killer-cell activity	
	* I.I.	# N	I.I.	N	I.I.	N	I.I.	N	I.I.	N	I.I.	N	I.I.	N	I.I.	N
All antibiotics		670	+0.04	309	–0.10	176	–0.36	70	+0.24	54	–0.03	39	–0.15	13	–0.11	9
Cefodizime	+0.60	45	+0.77	22	+0.14	7	+0.88	8		0	+0.60	5	0.00	2	–1.00	1
Erythromycin	–0.11	35	–0.27	15	–0.08	12	–1.00	2	+0.75	4	0.00	1	0.00	1		0
Clindamycin	+0.41	27	+0.36	14	+0.44	9	–1.00	1	+1.00	1	+1.00	1	+1.00	1		0
Roxithromycin	–0.14	21	–0.43	7	0.00	6	0.00	2	0.00	6		0		0		0
Cefotaxime	–0.42	19	–0.29	7	–0.80	5	–0.33	3	·	0	0.00	3	–1.00	1		0
Tetracycline	–0.53	17	–0.60	5	–0.25	4	–1.00	4	0.00	1	–0.33	3		0		0
Cefoxitin	+0.27	15	+0.40	9	+0.29	7	–1.00	1	+1.00	1	0.00	1		0		0
Amphotericin B	+0.24	17	+0.44	9	–0.33	3	0.00	2	+0.33	3		0		0		0
Imipenem	+0.71	14	+0.67	6	+1.00	5	+0.33	3		0		0		0		0
Rifampicin	–0.38	13	0.00	5	–0.75	4	–0.50	2		0	–0.50	2		0		0
Gentamicin	–0.46	13	–0.40	5	0.00	1	–1.00	2	0.00	2	0.00	1	–1.00	1	–1.00	1
Teicoplanin	–0.17	12	–0.14	7	–0.67	3		0	+1.00	1		0	0.00	1		0
Vancomycin	0.00	11	+0.14	7	0.00	2	–1.00	1		0		0	0.00	1		0
Ciprofloxacin	–0.09	11	0.00	2	0.00	1	–0.25	4	0.00	3	0.00	1		0		0
Josamycin	–0.09	11	0.00	3	+0.20	5		0		0	–0.67	3		0		0
Ampicillin	–0.40	10	–0.60	5	–0.50	2	0.00	1	0.00	1	0.00	1		0		0

* I.I.: "immune index" = number of positive statements/number of negative statements/total number of statements
# N: total of statements.

Zusammenfassung: Immunmodulierende Wirkungen von Antibiotika. Antibiotika können direkt mit dem Immunsystem in Wechselwirkung treten. Im Folgenden geben wir eine Übersicht über immunmodulierende Wirkungen von Antibiotika. Medline Datenbasen auf CD-ROM für die Jahre 1987–1994 mit den Stichworten "*thesaurus* explode antibiotics / all AND (*thesaurus* explode immune-system/ drug effects OR *thesaurus* immune-tolerance / drug effects)" wurden befragt. Die immunologischen Studien betrafen Aspekte der Phagozytenfunktionen: Phagozytose und Abtötung sowie Chemotaxis und Aspekte der Lymphozytenfunktion, Lymphozytenproliferation, Zytokinproduktion, Antikörperbildung, Überempfindlichkeitsreaktion vom verzögerten Typ und natürliche Killerzellaktivität. Um immunmodulierende Eigenschaften von Antibiotika quantifizierbar und vergleichbar zu machen, wurde ein wie folgt definierter "Immunindex" berechnet:

$$\frac{\text{Zahl positiver Aussagen} - \text{Zahl negativer Aussagen}}{\text{Gesamtaussagen.}}$$

Positive Wirkungen auf die Phagozyten wurden mit Cefodizim, Imipenem, Cefoxitin, Amphotericin B und Clindamycin gemacht. Bei Erythromycin, Roxithromycin, Cefotaxim, Tetracyklin, Ampicillin und Gentamicin wurden negative Effekte beobachtet. Clindamycin, Cefoxitin und Imipenem induzieren eine Verstärkung der Chemotaxis. Auf die Lymphozytenproliferation hat Cefodizim den stärksten Stimulationseffekt, Tetrazyklin hat den stärksten negativen Effekt. Die Wirkung auf Zytokinproduktion kann nur für Erythromycin und Amphotericin B beurteilt werden, bei allen anderen Substanzen reichen die Daten hierfür nicht aus. Erythromycin und Amphotericin B führen offensichtlich zu einer Stimulation der Zytokinproduktion. Auf die Antikörperbildung hat Cefodizim die stärkste positive Wirkung, deutlich negative Effekte wurden mit Josamycin, Rifampicin und Tetrazyklin beobachtet. Für die verschiedenen Antibiotika liegen nicht genügend Studien zur Überempfindlichkeitsreaktion vom verzögerten Typ oder zur Natural Killer Cell Aktivität vor. Drei der Antibiotika haben ausgeprägte fördernde Wirkung auf das Immunsystem (Imipenem, Cefodizim, Clindamycin), acht haben ausgeprägt immunsuppressive Wirkung (Erythromycin, Roxithromycin, Cefotaxim, Tetrazyklin, Rifampicin, Gentamicin, Teicoplanin und Ampicillin).

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Book Review

M. J. Blaser, P. D. Smith, J. I. Ravdin, H. B. Greenberg, R. L. Guerrant (eds.)
Infections of the Gastrointestinal Tract
1,610 pages, numerous illustrations and tables
Lippincott-Raven Publishers, Philadelphia 1995
Price: $ 282.00

This compendium dealing with the growing field of human gastrointestinal infections is divided into major sections containing 97 up-to-date review articles. The book represents the current state of knowledge provided by 162 contributors who are all experts in different aspects of human gastrointestinal infections. It is more than a theoretical approach, as it is rich in practical information about modern systems of diagnosis, therapy, prevention and control of gastrointestinal infections. The book is addressed to clinicians, microbiologists, epidemiologists and to those who are involved in all kinds of scientific research on infections of the gastrointestinal system. Furthermore it is also suitable as an important source of information for teaching personnel at universities and medical schools.

The large index and the well-organized table of contents divided into ten specific parts, each containing several chapters, make it easy to locate any specific subject of interest. The first chapters focus on the more clinical aspects of gastrointestinal infections, such as physiology, structure and immunology of the gastrointestinal system and clinical gastrointestinal syndromes in the healthy and in the immunocompromised host. A section is devoted to gastric infections with *Helicobacter pylori* and other gastric pathogens. The second half of the book presents a detailed description of the various infective agents, such as bacteria, viruses and parasites, their diagnosis and therapy, as well as the prevention and control of gastrointestinal infections.

The 97 individual chapters are generally concisely written, easily understandable and contain many comprehensive tables and black and white illustrations. The different chapters are designed as full and complete review articles. The many current and relevant reference citations, usually more than 100 per chapter, present an extra source of background information allowing readers a rapid extension of their knowledge on any specific field of interest. Personally, I would prefer the references in alphabetical order, which would allow a clearer overview of the references cited. However, in general each chapter supplies sufficient background information to allow the reader to understand the specific aspect without necessarily referring to other chapters. It might be inevitable that such a complete comprehensive work written by many authors sometimes contains duplicate information in different chapters.

This costly and heavy-weight compendium is probably not intended for the shelves of medical students, but should be made available in libraries of universities, hospitals and in any other institution dedicated to the field of gastrointestinal infections.

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