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ANTIBIOTICS IN LABORATORY MEDICINE

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Susceptibility to Antibiotics: Species Incidence and Trends

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The incidence of bacterial species in hospitals and communities and their antibiotic susceptibility are of major concern to clinicians, microbiologists, and epidemiologists. The most common measure for bacterial sensitivity is the minimal inhibitory concentration (MIC), a measure that partly describes the pharmacodynamics of an antibiotic, although it ignores the bactericidal activity, which is also of great importance for the clinical value of an antimicrobial drug. Furthermore, MICs reflect only results after overnight incubation and do not account for interactions occurring between the time of inoculation and the final reading. Because of the ease of assessing the MIC, it is common practice to use MIC data to describe the antibacterial activity of a drug toward a bacterium or the sensitivity of a bacterium to a drug. Although it is now generally accepted that a direct correlation of MICs with the pharmacokinetics of the drugs does not give a reliable interpretation for the outcome of chemotherapy, most clinicians can use these data in combination with knowledge of the specific drug and the underlying disease of patients as a guideline for antimicrobial chemotherapy. Unfortunately, there is still no simple formula for the prediction of antibacterial therapy. Some rules, however, seem to be accepted.

1. For β -lactam drugs the time for which the drug concentration exceeds the MIC is the most important parameter. An increase of the drug concentration does not result in a better outcome.
2. For aminoglycosides the concentration above the MIC is the most important factor. Increase of the drug concentration, which is of course limited by the toxicity of these drugs, results in a better outcome.
3. For the quinolones both the drug concentration and the period of the concentration above the MIC seem to be important.

To make antimicrobial therapy applicable and to avoid treatment of infections with inappropriate drugs, MIC data can then be translated into categories of suscepti-

bility. To avoid misunderstanding, clear-cut definitions are needed.

"Sensitive" describes the responsiveness of bacteria to antimicrobial drugs and thus reflects the activity of the drug toward the bacteria. A sensitive organism has low MICs, a less sensitive one has higher MICs.

"Susceptible" describes an interpretive category implying that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated.

"Resistant" describes an interpretive category of strains that are not inhibited by the usually achievable systemic concentrations of agent with normal dosage schedules and/or that fall in the range where specific microbial resistance mechanisms are likely and where clinical efficacy has not been reliable in treatment studies.

"Activity" describes the effectiveness of a drug toward bacteria, usually by means of MICs but also by killing curves, bactericidal titers, or minimal bactericidal concentrations (MBCs). Killing curves usually serve only during the period of drug development for a comparison of similar drugs. The everyday treatment, however, is not much influenced by these data.

Bactericidal titers can be extremely helpful with neutropenic patients, to monitor therapy. Dosing and the choice of drug can be adapted to the needs in adequate time. Furthermore, the evaluation of bactericidal titers can be very helpful in the understanding of treatment success.

Resistance and susceptibility to antimicrobial drugs are bacterial characteristics that are determined by genes either on the chromosome or on extrachromosomal elements such as resistance plasmids. The resistance characteristics are inherent in a bacterial cell but can be transferred by conjugation, transduction, and transformation. Plasmid-mediated resistance is more easily transferred than are chromosomal genes. The main reason for the distribution of resistance, however, is the clonal distribution of bacteria that grow easily and spread to other

individuals. The genetic event responsible for the emergence of resistance in any particular cell type is usually an extremely rare event. Consider, for example, the spread of penicillin-resistant *Neisseria gonorrhoeae* strains from the Far East to the western hemisphere. One or a few genetic events, rendering one *Neisseria* cell resistant to penicillin, was sufficient to select a resistant clone that spread around the world. Furthermore, resistance in hospitals is often due to an outbreak of a single pathogenic multiresistant strain, which later develops a number of genetic variants. The prerequisite for the emergence of resistant strains is the continuous selection pressure of antimicrobial use.

Clinicians, microbiologists, and epidemiologists use data on antibiotic activity against pathogens for their own specific needs. Very often susceptibility data showing the percentage of susceptible strains in one species are taken as a guideline. These data, however, do not provide information about the concentrations needed for inhibition, which is more important as a guide to chemotherapy. To enable easy access to the overwhelming amount of data available in the literature, this chapter is divided into six parts.

1. Incidence of species
2. Activity of antibacterial drugs
3. Sensitivity of bacteria.
4. Population distribution of MICs
5. Bactericidal concentrations
6. Proportion of susceptible strains in bacterial species.
7. International susceptibility of bacteria.

Parts 2 and 3, which deal with the activity of antibacterial drugs and the sensitivity of bacteria, are the most important ones, because they provide information for true comparison of the drugs. Tables 19.2 and 19.3 facilitate rapid comparison of antimicrobial activity toward a broad range of species. For drugs that have been in use for a long time, it is difficult to find data that are compatible with the scheme used. These data have therefore been adapted from the available literature. For clarity and balance, susceptibility data and data on the incidence of species are kept to a minimum, in view of the divergence of reports and epidemiology and the danger of manipulation and misinterpretation.

INCIDENCE OF SPECIES

The incidence of bacterial species isolated from all body sites of hospital patients indicates the importance of the species and provides information that is relevant to antimicrobial chemotherapy. The incidence in specific body sites enables calculation of the probability of occurrence of a given species in specific body sites when no isolate can be cultured before the onset of chemotherapy. Reports on the frequency of isolated species reflect the majority of cases and underestimate the impor-

tance of rarely isolated organisms that might cause specific infections. The number of isolated species never represents the true number of infecting organisms, because (a) material is not cultured from all patients, (b) the causative agent is not always isolated, (c) fastidious organisms are often overlooked, and (d) it is not possible to take samples from many sites.

The incidence of isolates changes according to the conditions. The specific epidemiologic expertise of a given hospital is as important as the methods of the microbiologic laboratory and the reporting habits. Shifts in the frequency of specific pathogens have often been reported and may be related to antibiotic usage. Such a trend is extremely difficult to prove, because large numbers of organisms over a continuous period of time are needed for statistical evaluation. Figure 19.1 includes the species most commonly isolated in the United States. The incidence of species isolated from all body sites in hospital patients in the United States is listed in Table 19.1.

ACTIVITY OF ANTIBACTERIAL DRUGS

In Table 19.2, 84 antimicrobial drugs are listed in seven groups: penicillins, cephalosporins, other β -lactams, quinolones, aminoglycosides, and other antimicrobial agents. In each group the drugs are listed in alphabetical order. The bacterial species tested differ from drug to drug because of the spectrum of activity of each and according to the authors' choice. Currently, data on the activity of antibacterials are published in most journals as the range of MICs, the 50% MIC (MIC_{50}), and the 90% MIC (MIC_{90}), and the same scheme is followed here. When data on a drug have been published by several authors, the most recent publications are included. Older publications have been avoided because of the difficulty of reading the MIC_{50} and MIC_{90} values from the original figures or tables.

SENSITIVITY OF BACTERIA

Table 19.3 lists 82 different species in alphabetical order. MIC_{50} , MIC_{90} , and the range of MICs are given as in Table 19.2, so the user can easily compare different

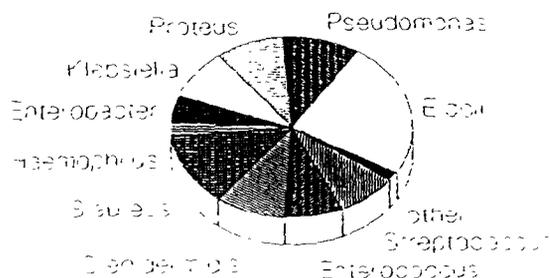


Figure 19.1 Incidence of species. Parts of the circle indicate the incidence of isolation of the most commonly isolated species. See Table 19.1 for data.

Table 19.2—continued

Species	n	Range ($\mu\text{g}/\text{mL}$)	MIC ₅₀ ($\mu\text{g}/\text{mL}$)	MIC ₉₀ ($\mu\text{g}/\text{mL}$)	Reference
Other antibiotics—continued					
Cotrimoxazole					
<i>Streptococcus pyogenes</i>	50	0.5–8	2	4	45
<i>Yersinia enterocolitica</i>	20	0.06–0.5	0.125	0.125	19
<i>Yersinia enterocolitica</i>	20	0.06–0.5	0.125	0.25	20
Doxycycline					
<i>Branhamella (Moraxella) catarrhalis</i> (non- β -lactamase producer)	14	≤ 1	≤ 1	≤ 1	49
<i>Branhamella (Moraxella) catarrhalis</i> (non- β -lactamase producer)	13	0.06–0.25	0.25	0.25	137
<i>Branhamella (Moraxella) catarrhalis</i> (β -lactamase producer)	47	≤ 1	≤ 1	≤ 1	49
<i>Branhamella (Moraxella) catarrhalis</i> (β -lactamase producer)	25	0.125–0.25	0.25	0.25	137
<i>Citrobacter diversus</i>	18	1–4	2	4	**
<i>Citrobacter freundii</i>	42	2–64	4	8	**
<i>Chlamydia trachomatis</i>	13	0.015–0.125	0.03	0.06	149
<i>Chlamydia trachomatis</i>	45	0.03–0.125	0.06	0.125	51
<i>Enterobacter aerogenes</i>	22	1–128	4	8	**
<i>Enterobacter cloacae</i>	51	1–32	4	4	**
<i>Enterococcus faecalis</i>	98	0.25–64	16	32	**
<i>Escherichia coli</i>	98	0.5–256	2	64	**
<i>Haemophilus ducreyi</i>	122	≤ 0.25 –64	2	32	28
<i>Haemophilus influenzae</i> (non- β -lactamase producer)	137	≤ 1 – ≥ 32	≤ 1	≤ 1	49
<i>Haemophilus influenzae</i> (β -lactamase producer)	46	≤ 1 –32	4	8	49
<i>Klebsiella oxytoca</i>	51	1–64	2	4	**
<i>Klebsiella pneumoniae</i>	94	0.5–256	4	32	**
<i>Morganella morganii</i>	48	2–256	4	32	**
<i>Proteus mirabilis</i>	98	4–128	32	32	**
<i>Proteus vulgaris</i>	49	0.5–512	4	32	**
<i>Providencia stuartii</i>	11	8–512	512	512	**
<i>Pseudomonas aeruginosa</i>	100	2–128	16	32	**
<i>Salmonella</i> spp	22	2–8	4	4	**
<i>Salmonella typhimurium</i>	12	4–512	4	256	**
<i>Serratia liquefaciens</i>	15	2–64	8	16	**
<i>Serratia marcescens</i>	28	2–256	8	32	**
<i>Staphylococcus aureus</i>	100	0.06–32	0.25	8	**
<i>Staphylococcus coagulase-negative</i>	58	0.06–16	0.5	2	**
<i>Ureaplasma urealyticum</i>	10	0.25–2	0.5	2	59
Erythromycin					
<i>Bacillus</i> spp	20	0.03–2	0.25	2	139
<i>Bacteroides fragilis</i>	97	≤ 0.25 –16	1	8	102
<i>Bordetella bronchiseptica</i>	11	4–32	8	32	86
<i>Bordetella parapertussis</i>	46	≤ 0.125 –4	0.25	0.25	86
<i>Bordetella pertussis</i>	32	1–0.5	0.25	0.25	188
<i>Bordetella pertussis</i>	75	≤ 0.125 –0.5	≤ 0.125	≤ 0.125	86
<i>Borrelia burgdorferi</i>	10	0.03–0.125	0.03	0.06	133
<i>Branhamella (Moraxella) catarrhalis</i>	20	≤ 0.125 –0.5	0.25	0.25	45
<i>Branhamella (Moraxella) catarrhalis</i>	20	0.125–0.5	0.25	1	75
<i>Branhamella (Moraxella) catarrhalis</i> (non- β -lactamase producer)	40	≤ 0.06 –0.5	0.25	0.5	148
<i>Branhamella (Moraxella) catarrhalis</i> (non- β -lactamase producer)	13	0.03–0.125	0.06	0.06	37
<i>Branhamella (Moraxella) catarrhalis</i> (non- β -lactamase producer)	14	≤ 0.06 –1	0.125	1	49
<i>Branhamella (Moraxella) catarrhalis</i> (non- β -lactamase producer)	16	0.015–1	0.06	0.25	34
<i>Branhamella (Moraxella) catarrhalis</i> (β -lactamase producer)	47	≤ 0.06 –1	0.25	0.5	49
<i>Branhamella (Moraxella) catarrhalis</i> (β -lactamase producer)	58	0.03–0.25	0.125	0.125	34
<i>Branhamella (Moraxella) catarrhalis</i> (β -lactamase producer)	160	≤ 0.06 –8	0.25	0.5	148