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Specialized Explanations for Dosage Selection

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In this chapter we describe specialized routines that MYCIN uses to evaluate and explain appropriate drug dosing. The processes that the program uses in its selection of antimicrobials and subsequent dosage calculations have been refined to take into account a variety of patient- and drug-specific factors. Originally, all dosage recommendations were based on normal adult doses. However, it was soon recognized that the program needed to be able to recommend optimal therapy by considering information about the patient, such as age and renal function, as well as pharmacokinetic variables of the drugs. The addition of an ability to customize doses expanded the capabilities of the consultation program.

Earlier chapters have described the way in which MYCIN uses clinical and laboratory data to establish the presence of an infection and the likely identity of the infecting organism(s). If positive laboratory identification is not available, MYCIN ranks possible pathogens in order of likelihood. Antimicrobials are then chosen to treat effectively all likely organisms. In order to select drugs to which the organisms are usually sensitive, MYCIN uses susceptibility data from the Stanford bacteriology laboratory. The program also considers the fact that the patient's previous antimicrobial treatment may influence an organism's susceptibility. MYCIN disfavors a drug that the patient is receiving at the time a positive culture was obtained.

Drug-specific factors are then considered before therapy is chosen. Some drugs, such as many of the cephalosporins, are not recommended for patients with meningitis because they do not adequately cross the blood-

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This chapter is an abridged version of a paper, some of which was originally presented by Sharon Wraith Bennett at the 12th Annual Midyear Clinical Meeting of the American Society of Hospital Pharmacists, Atlanta, Georgia, December 8, 1977, and which appeared in *American Journal of Hospital Pharmacy* 37: 523–529 (1980).

brain barrier and may lead to the development of resistance (Fisher et al., 1975). One antimicrobial may be selected over another, similar drug because it causes fewer or less severe side effects. For example, nafcillin is generally preferred over methicillin for treatment of staphylococcal infections because of the reported interstitial nephritis associated with methicillin (Ditlove et al., 1977). MYCIN'S knowledge base therefore requires continual updating with new indications or adverse reactions as they are reported in the medical literature.

Several patient-specific factors may further limit the list of acceptable antimicrobials. Tetracycline, for example, is not recommended for children (Conchie et al., 1970) or pregnant (Anthony, 1970) or breast-feeding (O'Brien, 1974) women. Also, prior adverse reactions to antimicrobials must be considered by the program.

19.1 Customizing Doses

Efficacious treatment of infectious diseases begins with selection of an antimicrobial; however, it is likely that the patient will not be cured unless the dose and the route of administration of the drug are appropriate. MYCIN takes into account the site of the infection, the age of the patient, and the patient's renal status in determining the dosage regimen for each drug.

Consider, for example, the importance of patient age in therapy planning. The half-life of some drugs may be longer in neonates than in adults because of the immaturity of the former's microsomal enzyme system and kidneys (Weiss et al., 1960). Therefore, the doses of these drugs, in mg/kg amounts, should be lower in the neonates than in the adults. On the other hand, some antimicrobials, such as gentamicin, may require a higher relative dose in children than in the adults, possibly because of a larger volume of distribution (Siber et al., 1975). MYCIN therefore uses different calculations when appropriate for determining doses for neonates, infants, children, and adults.

Most antimicrobials are fully or partially excreted by the kidneys; for this reason, it is necessary to consider the patient's renal function in order to determine a safe and effective regimen. The program uses the patient's creatinine clearance as an indicator of the degree of renal impairment. Doses are adjusted in patients over six months of age if the creatinine clearance falls below 80 ml/min/1.73 m^2 and if more than 15% of the drug is excreted unchanged in the urine. In children between one week and six months of age, the dose is changed if the creatinine clearance is less than 60ml/min/1.73 m^2. A creatinine clearance of 30ml/min/1.73 m^2 indicates

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47) Does John Jones have a clinically significant allergic reaction to any antimicrobial agent?
** NO
48) Do you have reason to suspect that John Jones may have impaired renal function?
** YES
49) What is the most recent creatinine clearance in ml/min which you feel is a true representation of John Jones's
    renal function?
** UNKNOWN
50) What is the most recent serum creatinine of John Jones (in mg/100ml)?
** 1.9
51) What is the previous serum creatinine of John Jones (in mg/100ml)?
** 1.8
52) Number of days between John Jones two most recent serum creatinines:
** 2
53) John Jones's weight in kilograms (or <number> POUNDS):
** 70
54) John Jones's height in centimeters (or <number> INCHES):
** 175
Estimated body surface area is 1.9 sq. meters.
Dosage adjustments will be based on the calculated creatinine
    clearance of 42.7 ml/min/1.73 sq. meters (adjusted to
    average body surface area).
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FIGURE 19-1 The patient's creatinine clearance is used as an indicator of the degree of renal function. When the creatinine clearance is not known, it is estimated from the age, sex, weight, and serum creatinine of the patient and adjusted to average body surface area before the dose is calculated.

renal impairment in infants[1] between one day and one week old (Edelmann and Barnett, 1971). Because of the passage of maternal creatinine into the infant serum at birth, no estimate of renal function is attempted if the newborn is less than one day old. For infants younger than six months, MYCIN warns the user of the large degree of possible error in the estimated doses because of the changing renal function and a poor relationship between glomerular filtration rate and body surface area (Rubin et al., 1949).

When the creatinine clearance of an adult patient is not known, it is estimated from the age, sex, weight, and serum creatinine (Jelliffe and Jelliffe, 1972) (Figure 19-1). For children less than 12 years of age, the height and serum creatinine are used to estimate the creatinine clearance (Schwartz et al., 1976). If two consecutive serum creatinines indicate rap-

[1]The creatinine clearance in infants is less than in adults because of decreased glomerular membrane permeability, smaller glomerular filtering surface, lower perfusion pressure, and lower renal plasma flow.

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[REC-1] My preferred therapy recommendation is:
Give the following in combination:
        1) CHLORAMPHENICOL
           Give: 1.75g (17.6 ml) q6h IV [calculated on basis of 25 mg/kg]
        2) GENTAMICIN
           After a loading dose of: 112 mg (2.8 ml, 80mg/2ml ampule) IV
                [calculated on basis of 1.6 mg/kg],
           give: 70 mg (1.8 ml, 80mg/2ml ampule) q8h IV [calculated on
                basis of 1.0 mg/kg] plus consider giving 5 mg q24h
                Intrathecal
           Or, after a loading dose of: 140 mg (3.6 ml, 80mg/2ml ampule)
                IV [calculated on basis of 2.0 mg/kg],
           give: 119 mg (3.0 ml, 80mg/2ml ampule) q14h IV [calculated on
                basis of 1.7 mg/kg] plus consider giving 5 mg q24h
                Intrathecal
                   [normal dose is 1.7 mg/kg q8h IV]
Would you like to enter a new dosing interval?
** YES
Please enter the number of hours.
** 12
           After a loading dose of: 133 mg (3.4 ml, 80mg/2ml ampule) IV
                [calculated on basis of 1.9 mg/kg],
           give: 105 mg (2.6 ml, 80mg/2ml ampule) q12h IV [calculated on
                basis of 1.4 mg/kg] plus consider giving 5 mg q24h
                Intrathecal
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FIGURE 19-2 MYCIN provides three different dosage regimens for each antimicrobial whose dose must be adjusted in renal failure. One method changes the dose, another alters the interval, and the third calculates a new dose given any interval.

idly changing renal function, a warning is printed, which recommends repeating the assessment of the degree of impairment before an accurate dosage regimen can be determined. The creatinine clearance is adjusted to average body surface area (Boyd, 1935) before the program calculates a dose (Figure 19-2). If the creatinine clearance indicates renal failure, MYCIN calculates doses based on the first-order pharmacokinetic properties of the antimicrobials (see Figure 19-2) and the patient's creatinine clearance. (A description of the formulas is included in Figure 19-4.)

The program provides three different dosage regimens for each antimicrobial whose dose must be adjusted. One method changes the dose, another alters the dosing interval, while the third calculates a new dose given any interval. This last option allows the physician to select a dosing interval that is convenient for the staff to follow and a dose that is a reasonable volume to administer. A loading dose is calculated for each regimen so that an effective blood level can be reached as soon as possible. The dose is provided in both a mg/kg amount and the number of milliliters, capsules, or tablets required (Figure 19-2).

If a patient's renal function changes during therapy, the physician can obtain a new dosage recommendation without repeating the entire infec-

tious disease consultation. A shortened version of the consultation will recalculate the doses on the basis of the patient's current renal function. The program will request only the information necessary for determining the new doses, such as the most recent creatinine clearance (or serum creatinine).

19.2 Selection of Dosage Regimen

Although it is widely debated which dosage regimen is best, it is generally recognized that the blood level of antimicrobials used to treat bacteremias should exceed the minimum inhibitory concentration (MIC) while remaining below toxic levels. The health professional must decide between allowing the drug level to fluctuate above and below the MIC and consistently maintaining the drug level above the MIC through more frequent dosing. This decision is based on a variety of factors including the organism identity and the drug under consideration. To aid the prescriber in selecting the most appropriate regimen, MYCIN generates a graph for each regimen showing the predicted steady-state blood levels over time (Figure 19-3) (Gibaldi and Perrier, 1975). The MIC of the organism and the toxic level of the drug (when they are available) are also included on the graph. The graph provides a rough estimate of the blood levels and the time of peak concentration in the patient. It is provided to improve the initial selection of a dosage regimen, not to replace the measurement of blood levels. Monitoring blood levels whenever they are available is strongly recommended.

19.3 Explanation of Recommendations

At the conclusion of the consultation, the physician can ask MYCIN simple questions to obtain assurance that the diagnosis and treatment are reasonable. These questions may refer to the current consultation or they may be general, regarding any of the system's knowledge. The program provides a justification for the therapy selection, which includes the reasons for selecting one antimicrobial instead of another. Also available is an explanation of the calculations used to decide on a dose (Figure 19-4). The physician can also ask to see relevant parts of MYCIN'S knowledge base, including justification and literature references (Figure 19-5).

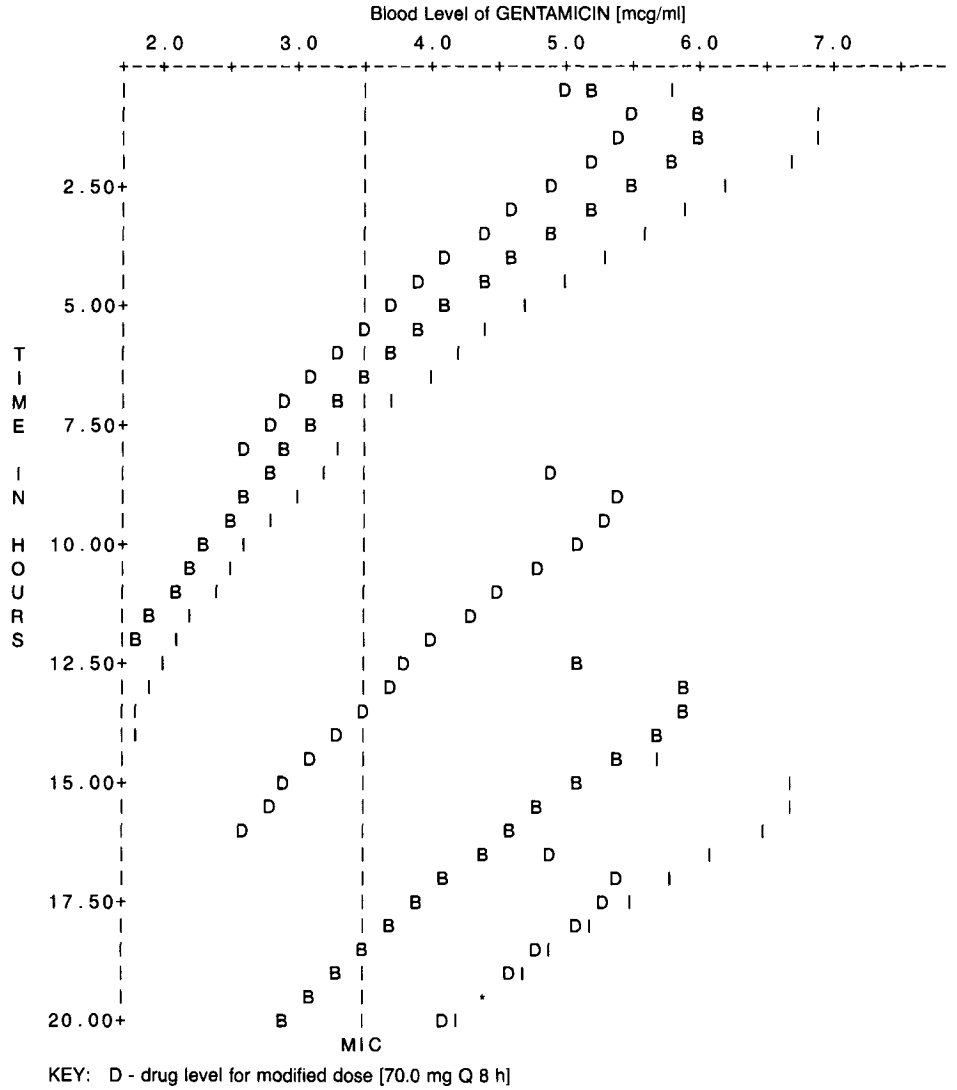

FIGURE 19-3 Graph of blood levels of a drug (gentamicin) over time for different doses and dose intervals. The graph is shown precisely as it is printed by the computer. Note that regimen I, with the longest dosing interval, reaches the highest blood levels episodically but also leaves the patient with blood levels below the MIC for the longest period of time. The somewhat atypical orientation of this graph, designed for terminal output, displays time vertically, blood level horizontally.

**** HOW DID YOU CALCULATE THE DOSE FOR GENTAMICIN?**

When GENTAMICIN is given for MENINGITIS, the recommended dosage is:
if age is > 2 yrs then 1.7 mg/kg q8h IV plus consider giving 5 mg q24h IT,
else 2.3 mg/kg q8h IV plus consider giving 2.5-4 mg/day IT.

The normal dose for John Jones is: 119 mg (3.0 ml, 80mg/2ml ampule) q8h IV
[calculated on the basis of 1.7 mg/kg] plus consider giving 5 mg q24h IT

GENTAMICIN is excreted by the kidneys, so its dosage must be modified in renal failure.

The following table shows how the patient's renal function was determined:

Identifier	Value	Definition
SCR1	1.9	the most recent serum creatinine (mg/100ml)
SCR2	1.8	the previous serum creatinine (mg/100ml)
CCr(f)	42.7	estimated creatinine clearance, adjusted for normal body surface area (ml/min/1.73 sq. meters)
CCr(n)	100	the average normal creatinine clearance for John Jones's age group
CCr(min)	80	the minimum normal creatinine clearance for John Jones's age group

Since CCr(f) < CCr(min), John Jones has renal impairment.

To modify the dosage of GENTAMICIN, the following pharmacokinetic parameters were used:

Identifier	Value	Definition
a	.007	the fraction hourly loss of a drug due to non-renal processes
b	.0022	the slope of the plot of the elimination rate constant of a drug versus the patient's creatinine clearance
Q	.57	the drug's elimination rate fraction: elimination rate of the drug as a fraction of the drug's "normal" elimination rate.

Q was calculated using the formula:

$$Q = [a + b * CCr(f)] / [a + b * CCr(n)]$$

My first dosage recommendation decreased the amount of GENTAMICIN and left the dosing interval unchanged. The new amount was calculated by multiplying the old amount by Q.

The second recommendation increased the dosing interval and left the amount of GENTAMICIN unchanged. The new interval was calculated by dividing the old interval by Q.

FIGURE 19-4 The physician can ask MYCIN questions to obtain assurance that the diagnosis, treatment, and dose are reasonable.

19.4 Summary and Conclusions

MYCIN is able to customize therapy recommendations by using its knowledge base in conjunction with patient-specific information. The large knowledge base contains facts about organism susceptibilities to drugs, ep-

** HOW DO YOU DETERMINE BODY SURFACE AREA?

RULE104

[This rule applies to any patient, and is tried in order to find out about the patient's estimated body surface area]

IF: 1) The weight of the patient is known, and
2) The height of the patient is known

THEN: Use Boyd's algorithm to calculate body surface area from weight and height [Boyd, E. The Growth of the Surface Area of the Human Body, 1935, pp 1–133.]

Author: Wraith

Justification: A comparative evaluation with statistical analysis of the Boyd method with the DuBois formula demonstrated that the Boyd formula is more accurate for abnormal body types. [Sendray J. et al., Determination of human body surface area from height and weight, Applied Physiology, 7(1):1-12, July 1954.]

FIGURE 19-5 The person obtaining a MYCIN consultation can see the decision rules that the program uses, including justification and literature references.

idemiology of infectious diseases, and pharmacokinetics and toxicity of various antimicrobials. This knowledge enables the program to determine appropriate treatment specific to a patient's age, renal function, and prior drug reactions. MYCIN'S explanation capability allows the user to analyze the process by which the program arrived at a therapy recommendation. This capability may also play an educational role by reminding the physician of critical factors to consider when prescribing therapy for other patients.

Increasing evidence of inappropriate antimicrobial therapy indicates a need for assistance in the expanding area of infectious disease therapy selection (Neu and Howrey, 1975). There is a recognized need for continuing education as well as for computational assistance with dosage adjustments in renal failure. This is not surprising when one recognizes all of the factors that must be considered in a therapy decision. One response to the problem of antimicrobial misuse is to increase the availability of consultations with infectious diseases experts. A consultation not only provides assistance in determining the appropriate therapy for the patient under consideration but also is an educational experience for the physician requesting it. Computer-based consultation programs such as MYCIN can provide medical professionals with clinical advice and educational information when human consultants are not available.