ASSIGNMENT 4

Infectious Disease

Aminoglycoside antibiotics are particularly useful clinically in the treatment of serious gram-negative bacillary infections among hospitalized patients. Despite their potential for toxicity, as well as the continued development of newer antimicrobial agents of other classes, it seems likely that the clinical use of aminoglycosides will continue to be widespread. The choice of a particular aminoglycoside antibiotic for a given patient depends on several factors, including the specific clinical situation, differences in antimicrobial spectrum and cost, and risks of side effects, particularly nephrotoxicity and auditory toxicity. Many randomized, controlled trials have been published that compare the various aminoglycoside antibiotics with respect to efficacy, nephrotoxicity, and, to a lesser extent, auditory toxicity. These individual trials have varied widely with respect to their design features and their conclusions. A major limitation to their interpretability is that the majority of the individual trials have lacked an adequate sample size to detect the small to moderate differences between treatment groups that are most plausible. As a result, the individual trials published to date have generally not permitted firm conclusions, especially concerning the relative potential for toxicity of aminoglycosides.

In these circumstances, one method to estimate the true effects of these agents more precisely is to conduct an overview, or *meta-analysis*, of the data from all randomized trials. In this way, a true increase in risk could emerge that otherwise would not be apparent in any single trial due to small sample size. Therefore, a quantitative overview of the results of all published randomized controlled trials that assessed the efficacy and toxicity of individual aminoglycoside antibiotics was undertaken.

Forty-five randomized clinical trials, published between 1975 and September 1985, were identified that compared two or more of five aminoglycoside antibiotics: amikacin, gentamicin, netilmicin, sisomicin, and tobramycin. Thirty-seven of these trials could provide data suitable for comparative purposes.

The specific endpoints of interest were efficacy, nephrotoxicity, and auditory toxicity. Efficacy was defined as bacterial or clinical response to treatment as reported in each individual trial. Nephrotoxicity was defined as the percentage of toxic events to the kidney reported, whether or not the published paper suggested some explanation other than the use of the study drug, such as use of another potentially nephrotoxic agent, or the presence of an underlying disease affecting kidney function. Auditory toxicity was defined as reported differences between pre- and post-treatment audiograms.

The data are organized into three Data Sets: EFF.DAT, NEPHRO.DAT, and OTO.DAT, all on the data disk. A separate record is presented for each antibiotic studied for each endpoint. The format is given in the files EFF.DOC, NEPHRO.DOC, and OTO.DOC, on the data disk.

Columns 1–8: Study name
10–11: Study number (number on reference list)
13: Endpoint (1 = efficacy; 2 = nephrotoxicity; 3 = ototoxicity)
15: antibiotic (1 = Amikacin; 2 = Gentamicin; 3 = Netilmicin; 4 = Sisomicin; 5 = Tobramycin)
17–19: Sample size
21–23: Number cured (for efficacy) or number with side effect (for nephrotoxicity or oxotoxicity)

Construct a model in BUGS to estimate the effect of each antibiotic on nephrotoxicity. Are there specific antibiotics you would recommend or not if you were statistical advisor to a hospital infection-control committee?