A MODEL FOR EFFECTIVE MONITORING OF PATIENTS RECEIVING AMINOGLYCOSIDE ANTIBIOTIC THERAPY

by

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THE UNIVERSITY OF UTAH GRADUATE SCHOOL

SUPERVISORY COMMITTEE APPROVAL

of a thesis submitted by

Frances Gillen Gibbs

This thesis has been read by each member of the following supervisory committee and by majority vote has been found to be satisfactory.

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Linda S. Tyl
To the Graduate Council of the University of Utah:

I have read the thesis of Gillen Gibbs in its final form and have found that (1) its format, citations, and bibliographic style are consistent and acceptable; (2) its illustrative materials including figures, tables, and charts are in place; (3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Graduate School.

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ABSTRACT

Monitoring a patient's serum aminoglycoside levels is essential for reaching therapeutic levels of the drug while avoiding the adverse consequence of nephrotoxicity. In 1985, aminoglycoside testing at the University of Utah Health Sciences Center was evaluated by a pharmacy resident who reported that some patients had excessive numbers of tests performed while others experienced inadequate monitoring.

A committee was established to examine this perceived problem. The committee developed guidelines for aminoglycoside use which identified patients needing to be monitored and the number of levels to be performed. A new laboratory-ordering worksheet was designed to resolve specimen collection problems. Data collected on 146 patients, 71 prior to and 75 following implementation of the guidelines, were evaluated to assess the difference in the ordering patterns. In each group, PRE and POST, there were 50 patients who met the guideline criteria for being monitored. Serum creatinine levels were evaluated to assess compliance with the guidelines which recommended they be performed every three to four days during therapy as an indicator of aminoglycoside-associated nephrotoxicity.
A significant (P<.05) improvement in the ordering pattern for serum levels at 72 hours resulted after the guidelines were implemented. No change was seen in the ordering pattern of weekly serum levels. There was an 8% PRE and a 14% POST incidence of aminoglycoside-associated nephrotoxicity. The laboratory-ordering worksheets were submitted with 59% of the serum levels ordered and, when available, aided in the resolution of any problems. All hospital departments involved with aminoglycoside therapy had influence and control over the final solutions which aided in their acceptance of the changes.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>ix</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>4</td>
</tr>
<tr>
<td>Mode of Action</td>
<td>5</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>5</td>
</tr>
<tr>
<td>Toxicity</td>
<td>6</td>
</tr>
<tr>
<td>Dosage</td>
<td>9</td>
</tr>
<tr>
<td>Monitoring and Evaluation</td>
<td>11</td>
</tr>
<tr>
<td>Implementation of Guidelines and Laboratory-ordering Form</td>
<td>14</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td>15</td>
</tr>
<tr>
<td>Aminoglycoside Review Committee</td>
<td>15</td>
</tr>
<tr>
<td>Data Collection</td>
<td>18</td>
</tr>
<tr>
<td>Laboratory Testing</td>
<td>19</td>
</tr>
<tr>
<td>Creatinine</td>
<td>21</td>
</tr>
<tr>
<td>BUN</td>
<td>22</td>
</tr>
<tr>
<td>Evaluation of Data</td>
<td>22</td>
</tr>
<tr>
<td>RESULTS</td>
<td>25</td>
</tr>
<tr>
<td>Guidelines</td>
<td>25</td>
</tr>
<tr>
<td>Analysis of Data</td>
<td>36</td>
</tr>
<tr>
<td>DISCUSSION AND RECOMMENDATIONS</td>
<td>38</td>
</tr>
<tr>
<td>Laboratory</td>
<td>41</td>
</tr>
<tr>
<td>Nursing</td>
<td>41</td>
</tr>
<tr>
<td>Quality Assurance</td>
<td>42</td>
</tr>
<tr>
<td>Aminoglycoside Review Committee</td>
<td>42</td>
</tr>
<tr>
<td>APPENDIX A: GUIDELINES FOR AMINOGLYCOSIDE MONITORING IN ADULT AND PEDIATRIC PATIENTS GREATER THAN 44 WEEKS POSTCONCEPTUAL AGE</td>
<td>43</td>
</tr>
<tr>
<td>APPENDIX B: GUIDELINES FOR AMINOGLYCOSIDE USE AND MONITORING IN NEONATES</td>
<td>46</td>
</tr>
<tr>
<td>Appendix</td>
<td>Title</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>C</td>
<td>ARUP Worksheet</td>
</tr>
<tr>
<td>D</td>
<td>Aminoglycoside Dosing Chart</td>
</tr>
<tr>
<td>E</td>
<td>ARUP &quot;Hot Line&quot;</td>
</tr>
<tr>
<td>F</td>
<td>Committee Capsules</td>
</tr>
<tr>
<td>G</td>
<td>Associated and Regional University Pathologists, Inc. Clinical Microbiology Laboratory Procedure Manual, Section III</td>
</tr>
<tr>
<td>H</td>
<td>NCCLS Suggested Groupings</td>
</tr>
<tr>
<td></td>
<td>REFERENCES</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Patients Meeting Guideline Criteria for Serum Monitoring</td>
<td>26</td>
</tr>
<tr>
<td>2.</td>
<td>Patients Within and Without the Guidelines for Monitoring Aminoglycoside</td>
<td>27</td>
</tr>
<tr>
<td>3.</td>
<td>Days of Therapy and Number of Serum Levels Within and Without the Guideline Criteria</td>
<td>29</td>
</tr>
<tr>
<td>4.</td>
<td>Aminoglycoside-associated Nephrotoxicity for Patients Within and Without the Criteria for Monitoring both Pre- and Postimplementation of the Guidelines</td>
<td>30</td>
</tr>
<tr>
<td>5.</td>
<td>Compliance in the Use of Laboratory-ordering Worksheets</td>
<td>33</td>
</tr>
<tr>
<td>6.</td>
<td>Data for Cystic Fibrosis Patients</td>
<td>37</td>
</tr>
</tbody>
</table>
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INTRODUCTION

A clinical pharmacy resident at the University of Utah Health Sciences Center (UUHSC) reported that within a two-month period beginning in July 1985, 9 of 15 patients had inconsistent serum aminoglycoside levels. Results that seemed questionable included trough levels higher than peak levels, trough and peak levels increasing on the same dose and peak levels being drawn during the distributive phase. Drug doses were inappropriately changed because of the erroneous results. The timing of drug infusion and the collection of blood specimens were incorrectly recorded and occasionally assays were performed after the drug had been discontinued. This report by the clinical pharmacy resident suggested that the problems were primarily in the clinical laboratory.

As a result of this earlier report, an aminoglycoside review committee was established to attempt to resolve the problems. The committee included representatives from Pharmacy, Clinical Laboratory, Nursing, Quality Assurance, Obstetrics and Gynecology, Medicine, Surgery, Pediatrics and Nephrology. The committee formulated guidelines for the types of patients requiring monitoring and the appropriate number of levels to be tested, and designed a new laboratory-ordering worksheet. The guidelines and
laboratory-ordering worksheet are described in the methods and materials section and detailed in Appendices A - C.

As a monitoring and evaluation effort, the Joint Commission on Accreditation of Health Care Organizations requires drug usage evaluation of aminoglycosides. Drug usage evaluation seeks to identify trends and patterns and correct inappropriate drug use for an entire institution rather than on a patient-by-patient basis. When the review is conducted on a prospective or concurrent basis, results may also be of value to the individual patient. The primary goal is to monitor, evaluate and assure appropriate drug use. Solutions to the problems associated with one type of drug are often useful in solving problems associated with other drugs.

Under prospective payment systems, hospital laboratories are cost centers and must be managed in a cost-efficient manner. However, an administrative approach that focuses only on internal laboratory improvements is not the optimal solution. There must be appropriate integration of laboratory services into the patient care process. A coordinated effort by all of the departments represented on the aminoglycoside review committee was necessary to change the atmosphere from one of fault-finding to one of problem-solving. Once solutions were reached through the formulation of guidelines and the laboratory-ordering worksheet, education of physicians, nurses and laboratory personnel was initiated. The fact that each area involved was a
party to the solutions increased the acceptance of the changes.
BACKGROUND

The term aminoglycoside is applied to a group of antimicrobial drugs sharing common chemical, pharmacologic, and toxic features. The aminoglycosides included in this study are amikacin, gentamicin and tobramycin. No other aminoglycoside was used systematically during this study period. Generally, they are broad-spectrum antibiotics active against many gram-positive and gram-negative bacteria, which may cause a wide variety of serious infections including bacteremia, urinary tract infections, pneumonia, peritonitis, osteomyelitis, infected burns, ventriculitis, meningitis, and certain pelvic infections.10,11

Aminoglycosides have a marked affinity for the renal cortex and may accumulate in this tissue and cause extensive alteration of the proximal tubular cells, which can lead to nephrotoxicity most frequently manifested by proteinuria or azotemia.10 An increased prevalence of toxic effects with prolonged use is reported.10-12 Monitoring the patient's serum drug levels is essential for reaching therapeutic levels while avoiding the adverse consequence of nephrotoxicity.
**Mode of Action**

Aminoglycosides are bacterial antimicrobials that induce cell death by eliciting the formation of defective proteins by susceptible bacteria. To be effective, the drug must pass through the cell wall into the cytoplasm, bind irreversibly to the 30S unit of the ribosome and inhibit protein synthesis by blocking the recognition step, leading to misreading or miscoding of ribosomal RNA. Nonfunctional protein results due to the incorporation of improper amino acid sequences into peptides, which leads to cell death. The immunological competence of the host and the pathogenicity of the infecting organism are important factors in achieving the desired antibacterial response.

**Pharmacokinetics**

Aminoglycosides are generally administered intravenously as secondary infusions by a syringe pump over 20 minutes or in minibags over 30-60 minutes. The drug is poorly absorbed when administered orally. Topical absorption is also poor, but use of large topical doses over long periods of time may lead to substantial serum drug concentration.

Aminoglycosides are minimally protein-bound and because of their lipophobic nature, are distributed principally in the extracellular fluid. Because the dose is based on lean body weight, care must be taken to account for conditions with excessive extracellular fluid. In general, all aminoglycosides have a marked affinity for the
renal cortex and may accumulate in this tissue in concentrations 50-100 times those of plasma. The metabolic degradation of these antimicrobials has not been established.\textsuperscript{10}

Excretion of aminoglycosides is mainly by glomerular filtration. They are not metabolized and 85% to 95% of an administered dose is excreted unchanged, resulting in extremely high urinary concentration of the drug.\textsuperscript{13}

Toxicity

Aminoglycosides cause extensive alteration of proximal tubular cells of the nephron. There can be both morphologic and functional changes that lead to necrosis. Early toxicity is manifested by an increase in the excretion of $\beta_2$-microglobulin and other renal tubular enzymes, progressing to oliguric renal failure. Increased dose or prolonged treatment induces an array of tubular alterations including the release of brush border and lysosomal enzymes, mitochondrial alterations, focal tubular necrosis and regeneration, and alteration of the tubular function.\textsuperscript{10,13} De Broe, et al. describe animal studies which have demonstrated a sequence of events (time- and dose-dependent) going from lysosomal alterations, tubular dysfunction, focal cell necrosis, and luminal obstruction up to late renal excretory failure. This pattern has also been observed in humans when cultured cells exposed to gentamicin lyse when lysosomal overloading becomes extensive.\textsuperscript{14}
Other mechanisms of aminoglycoside toxicity toward proximal tubular cells, independent of lysosomes, and based on in vitro studies have been postulated, such as inhibition of "phosphotidyl inositol response,"\textsuperscript{15} mitochondrial dysfunction,\textsuperscript{16} or inhibition of Na\textsuperscript{+}/K\textsuperscript{+} ATPase.\textsuperscript{17}

Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe.\textsuperscript{10} Aminoglycoside nephrotoxicity is infrequent (8\% to 26\% of patients), usually mild, and generally reversible once doses of the offending drugs are adjusted or discontinued. In patients with diminished renal function, topical application of the drug may cause toxicity.\textsuperscript{13}

Ototoxic effects have also been attributed to aminoglycoside therapy. Eighth cranial nerve damage may be manifested by vestibular symptoms such as dizziness, nystagmus, vertigo and ataxia which are more frequently associated with streptomycin, gentamicin or tobramycin. Auditory (cochlear) symptoms such as tinnitus, roaring in the ears and varying degrees of hearing impairment are more frequently associated with amikacin, kanamycin, neomycin or paramomycin.\textsuperscript{10,11} Woods reported that damage to the eighth cranial nerve could be related to elevated serum trough values. Aminoglycosides diffuse into the inner ear fluids slowly and diffuse out with a half-life of decline in inner ear fluid concentrations slower than that in serum.\textsuperscript{13} The incidence of nephrotoxicity and ototoxicity has generally been reported at 2\% to 10\% of patients.\textsuperscript{12} This may be due
to poor elimination by the kidneys which allows more drug to diffuse into the inner ear. Significant hearing loss is seen in less than 1% of patients.

Miscellaneous, infrequent adverse effects of these drugs include malabsorption syndromes, neurotoxic pain and parathesias, acute brain syndrome, blurred vision, optic neuritis, depression of cardiac function, and elevation of serum enzymes representative of liver function (SGOT, SGPT, and alkaline phosphatase), nausea and vomiting, anemia and hypotension.

This study focused on the adverse consequence of aminoglycoside-associated nephrotoxicity as assessed by serum creatinine increases.

There are a number of documented drug interactions with aminoglycosides. There is significant danger of potentiation of adverse effects when drugs having similar action or toxicity are employed concomitantly. The use of cephaloridine in conjunction with aminoglycosides is a potentially lethal combination because of synergism of their nephrotoxic effects. Carbenicillin or ticarcillin used in conjunction with gentamicin will enhance the antibiotic in vivo; however, there may be an inhibitory effect when the compounds are administered through a common intravenous bottle and line. Concomitant therapy with other potentially nephrotoxic drugs should be carefully monitored. These drugs include potent diuretics (furosemide, bumetanide, ethacrynic acid and mannitol), non-
steroidal anti-inflammatory drugs, and other nephrotoxic antibiotics (bacitracin, polymyxin B, colistin, vancomycin, amphotericin B) and cyclosporin.11

Gentamicin is incompatible in solution with heparin with which it reacts to form a precipitate.10 Riley has reported studies showing that an immediate precipitate results when 20,000 units of heparin sodium is mixed with 320 mg of gentamicin sulfate.19

Patients in this study receiving aminoglycosides in addition to any other drugs that may interact will fall under the guidelines which require that their serum aminoglycoside levels be monitored.

Dosage

The appropriate dose of aminoglycosides is essential for reaching therapeutic levels of the drug while avoiding the adverse consequence of toxicity. Volume of distribution is important when aminoglycoside therapy is initiated. An appropriate initial (loading) dose can produce a therapeutic concentration throughout the total volume in which the drug distributes. Just as the volume of distribution is the most important factor in determining an adequate loading dose, elimination is most important in determining the maintenance dose.13

An increased concern with aminoglycosides is the apparent interpatient variability in serum levels resulting from the routine use of recommended dosage regimens. Since these drugs equilibrate with the physiological space
resembling the extracellular fluid compartment, patients with pathophysiological changes will have altered distribution volumes. Patients with peritonitis, congestive heart failure (CHF), and obesity will have a large distribution volume and require a larger dose to achieve therapeutic concentration. Conversely, clinically dehydrated patients have a low distribution volume and require less drug to reach optimal concentrations. As the pathophysiological changes are corrected, the distribution volumes may return toward normal, requiring dosage changes even though renal function does not change.\textsuperscript{12}

The UUHSC pharmacy provides the following information for an approximation of the loading dose. These dosage recommendations are adapted from Sarubbi and Hull.\textsuperscript{20}

\textbf{Amikacin:} 5-7.5 mg/kg (lean body weight)

\textbf{Gentamicin and Tobramycin:} 1.5-2 mg/kg (lean body weight)

Calculation of lean body weight for obese patients is necessary because the distribution of aminoglycosides is altered due to the differences in extracellular fluid content between fat and other tissues.\textsuperscript{18,21} Serum level monitoring is indicated in obese patients. One estimate of ideal (lean) body weight can be calculated as follows:\textsuperscript{20}

\begin{align*}
\text{Lean body weight (male) } &= 50 \text{ kg } + 2.3 \text{ kg (each inch } >5 \text{ ft.)} \\
\text{Lean body weight (female) } &= 45.5 \text{ kg } + 2.3 \text{ kg (each inch } >5 \text{ ft.)}
\end{align*}
The following formula is then used to calculate lean body weight for obese patients:22-25

(Total body weight - lean body weight) x 40% + lean body weight

Calculation of the maintenance dose\textsuperscript{11,20,26} is based on the creatinine clearance and a percentage of the loading dose required for the dosage interval selected. Creatinine clearance (Cr\textsubscript{Cl}) is calculated using the following formulas:\textsuperscript{27}

\text{Male Cr\textsubscript{Cl} (ml/min) = \frac{(140-age) \times weight (kg)}{serum creatinine (mg/dl) \times 72}}

\text{Female Cr\textsubscript{Cl} (ml/min) = 0.85 \times Male Cr\textsubscript{Cl} (ml/min)}

Guidelines described by Sarubbi\textsuperscript{20} for the calculation of the maintenance dose are detailed in Appendix D.

**Monitoring and Evaluation**

The Joint Commission requires an ongoing monitoring and evaluation of selected drugs that (1) may cause adverse reactions, or interact with other drugs in a manner that presents a serious health risk, (2) are used in the treatment of patients who may be at high risk for adverse reactions, or (3) have been designated through quality assurance activities for monitoring.\textsuperscript{1} In recent years, the use of serum drug levels has become an increasingly popular method of individualizing drug therapy.\textsuperscript{28} Careful monitoring of the patients is warranted for the following
reasons: (1) the lack of predictable serum levels of drug even when a nomogram is used to select the dose and dosing interval, (2) clinical response is achieved by reaching a therapeutic level, and (3) the documented relationship between some combination of drug dose, duration of therapy and toxicity. Monitoring drug levels has become a significant tool in the safe maintenance of patients.

A number of assay techniques are currently used for therapeutic drug monitoring. Microbiological bioassays use *Bacillus subtilis* or a similar micro-organism embedded in agar. Patient serum is placed into circular wells cut into the agar. After incubation, the zone of inhibition around the well is measured to determine the concentration of antibiotic in the serum. Although this method is inexpensive and available in most hospital settings, it exhibits some variation due to pH and the ion concentration of the agar, the strain of micro-organism used for testing, incubation time and temperature, and other antibiotics present in the sample being tested. It also requires a minimum of four to six hours of incubation time and may take 24 to 48 hours.

Radioimmunoassay (RIA), fluorescent immunoassay, fluorescent polarization immunoassay and enzyme immunoassay techniques all use antigen-antibody reactions to determine antibiotic concentrations in serum. They have a high degree of precision and specificity. Because of equipment requirements, these assays generally cost more than the
bioassay. However, they give quick, accurate, reproducible results with a very small sample size.

Aminoglycosides may also be measured by gas-liquid chromatography or high performance liquid chromatography. However, the high cost of these methods means that they are more often used in research settings than in clinical laboratories.13

Serum creatinine or creatinine clearance determinations may be useful in assessing the elimination of aminoglycosides. Because creatinine clearance approximates the glomerular filtration rate, serum creatinine may be used to estimate the drug clearance. Large increases in blood urea nitrogen (BUN) and serum creatinine will be noted as renal failure develops.13 In this study patients were considered nephrotoxic when serum creatinine concentrations increased ≥0.5 mg/dl when the baseline value was ≤3.0 mg/dl or increased ≥1.0 mg/dl when the baseline value was ≥3.0 mg/dl. Baseline serum creatinine values were defined as the mean of the last available measurements (up to three stable values) obtained within seven days before the initiation of aminoglycoside therapy. The serum creatinine levels must have begun to increase during the drug treatment or within 48 hours after the termination of therapy and remained elevated for two consecutive determinations in order to define the patient as having nephrotoxicity.29 Serum creatinine levels measured every three to four days are warranted.13
Urinalysis reports were evaluated for a decrease in specific gravity and proteinuria, and increases in serum BUN levels were observed as additional indicators of renal impairment. The final reports of microbiology cultures and their sensitivities were evaluated to assess the appropriateness of the selected antibiotic.

**Implementation of Guidelines and Laboratory-ordering Form**

Approximately one-third of laboratory tests are ordered for monitoring purposes. The overutilization of therapeutic drug monitoring adds excess cost to the patient's health care and underutilization of therapeutic drug monitoring may increase the risk of toxicity or subtherapeutic levels which also adds excess cost to the patient.

Teaching cost-effective laboratory utilization is an increasingly important issue confronting medical educators. It is well established that knowledge of the cost of a specific test will not necessarily alter the decision for ordering. Freeborn, et al. found that effective laboratory utilizers tended to have been trained in "well-established" medical schools. A critical approach to test laboratory utilization and interpretation must be conveyed to physicians in training if a lifelong pattern of effective resource utilization is to be established. The guidelines for monitoring were established with the quality of patient care as the objective.
MATERIALS AND METHODS

Aminoglycoside Review Committee

The aminoglycoside review committee included representatives from Pharmacy, Clinical Laboratory, Nursing, Quality Assurance, Obstetrics and Gynecology, Medicine, Surgery, Pediatrics and Nephrology. The group met monthly for approximately 18 months to develop guidelines, design the laboratory-ordering worksheet and implement the new program.

Guidelines for monitoring. The aminoglycoside review committee determined that drug peak and trough levels are indicated in the following situations:

1. therapy anticipated to continue >8 days
2. therapy anticipated to last <8 days if one or more of the following risk factors is present:
   a. age >60 years if therapy is anticipated to continue >3 days
   b. ICU status with suspected or proven bacteremia
   c. >10 cumulative days of aminoglycoside therapy within the preceding 3 months
   d. serum creatinine >1.2 mg/dl in creatinine clearance <70 ml/min in adults
   e. significant liver disease
f. shock or severe intravascular volume depletion

g. concomitant therapy with other potentially nephrotoxic drugs, such as:

(1) loop diuretics
(2) nonsteroidal anti-inflammatory drugs
(3) Amphotericin B
(4) Cyclosporin A

h. cystic fibrosis

i. refractory hypokalemia

j. other clinical situations that may imply decreased renal perfusion or altered volume of distribution

If patients receiving aminoglycosides are in any of the above categories, the initial serum peak and trough levels should be obtained within the first 72 hours of therapy. If no dosage adjustments are required and major physiologic parameters remain unchanged, levels may be followed on a weekly basis.

The peak serum level should be drawn approximately 30 minutes after the completion of the infusion of the drug. The trough level is usually drawn within 30 minutes of the next drug infusion. As long as the times of the sample collections for the peak and trough levels and drug infusion are known, the levels can be calculated.
These guidelines represent minimal criteria. Individual clinical circumstances may suggest more frequent or intensive surveillance.

The floor nurses were responsible for the administration of the aminoglycosides and notification of the laboratory of the appropriate times for samples to be drawn. The laboratory phlebotomists were responsible for collecting the samples at the appropriate times. Integration of the services of the physicians, nurses, and laboratory was required for effective utilization of aminoglycoside monitoring. Information regarding the new policies was disseminated through the laboratory and pharmacy newsletters which have been included as Appendices E and F. The pharmacy newsletter was distributed to the nurses and housestaff. Inservice presentations by members of the aminoglycoside review committee were given to all of the laboratory phlebotomists and all of the nurses on the medical service that was selected for the pilot program. Presentations regarding the guidelines and use of the laboratory-ordering worksheet were made to all head nurses who then instructed their staff prior to the guidelines being implemented. Comments were invited so that all of the areas involved would have a sense of responsibility for helping to make it work. Members of the aminoglycoside review committee were available for consultation.
Laboratory-ordering worksheet. Laboratory services for UUHSC are provided by Associated Regional and University Pathologists, Inc. (ARUP). The laboratory-ordering worksheet designed by the aminoglycoside review committee was used to provide information for the calculation of serum levels and to troubleshoot problems.

Addressograms were used to provide patient information on each laboratory-ordering worksheet. The ward clerk or nurse provided the name of the physician, service, drug to be determined, and whether trough, peak or both specimens were required. The time and dose of the last infusion for trough levels and the dose and time of the next dose were recorded for peak levels. The phlebotomist recorded the date and time the specimens for peak and trough levels were collected. Each person involved (nurses and phlebotomists) signed his or her name or identification number so that any problems could be traced and corrected. The laboratory-ordering worksheet was taken to the laboratory with the last sample drawn.

Data Collection

Charts of patients receiving aminoglycoside therapy were monitored every other day concurrent with therapy. Names and locations of the patients were obtained from the pharmacy in the morning before the drugs had been sent to the floors. During the period of April 19, 1987 through June 24, 1987, data were collected on 71 patients, 50 of whom satisfied criteria specified in the guidelines. The
guidelines were implemented in September 1987. Prior data were compared with data collected during the period of October 26, 1987 through January 4, 1988 on 75 patients, 50 of whom satisfied criteria specified in the guidelines.

Data collected included name, medical record number, admission date, service, diagnosis and other medications listed in the guidelines. Information collected included the specific aminoglycoside, regimen, peak and trough values if performed, BUN, serum creatinine, abnormal urinalysis results, and the final microbiology reports. Figure 1 is a representation of a data collection sheet.

**Laboratory Testing**

**Therapeutic drug monitoring.** Fluorescence polarization immunoassays were used for tobramycin and enzyme immunoassays were used for amikacin and gentamicin. Fluorescence polarization immunoassay depends on a biologically produced antibody that reacts specifically with the drug responsible for its production. A sample of an unknown quantity of drug competes with a known quantity of labeled drug for binding sites on the antibody. The labeled drug has a tracer that can be quantified by a given measurement technique. When the amount of bound tracer is measured, it can be used to quantitate the amount of drug present. This procedure is performed on the TDx® Analyzer. The coefficient of variation (CV) within runs is 3.1% at 1.0 μg/ml, 3.0% at 4.0 μg/ml and 2.9% at 8.0 μg/ml.
**NAME**  John Doe, 85 years old  
MRN  123 4567-8  
ADM DATE  10/30/81  
SERVICE  SICU

**DIAGNOSIS**  Diverticulitis

**DRUG**  Gentamicin  
**REGIMEN**

**CULTURES**  
Fluid-pelvic 3+ gr(-) rods amikacin 8, ampicillin 8, gentamicin 8

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<td>11/4</td>
<td>1812 4.1º</td>
<td>1800 1.9</td>
<td>17</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/5</td>
<td></td>
<td></td>
<td>21 H</td>
<td>1.4</td>
<td>100 q 12º</td>
<td></td>
</tr>
<tr>
<td>11/6</td>
<td>1035 4.1º</td>
<td>0840 1.4</td>
<td>21 H</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/7</td>
<td></td>
<td></td>
<td>21 H</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/8</td>
<td>1100 4.3º</td>
<td>0700 2.5º</td>
<td>21 H</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/9</td>
<td></td>
<td></td>
<td>27 H</td>
<td>1.1</td>
<td>80 q 12º</td>
<td></td>
</tr>
<tr>
<td>11/10</td>
<td>1430 7.2º</td>
<td>1130 1.2</td>
<td>25 H</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/11</td>
<td></td>
<td></td>
<td>21 H</td>
<td>1.2</td>
<td>D/C all antibiotics</td>
<td></td>
</tr>
<tr>
<td>11/12</td>
<td></td>
<td></td>
<td>17</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Medications:  ampicillin, clindamycin

**Figure 1**  
Sample Data Collection Sheet
Reference range:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Level</th>
<th>Trough Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>5-10 µg/ml</td>
<td>0.5-2.0 µg/ml</td>
</tr>
</tbody>
</table>

Amikacin and gentamicin levels are determined using the aca® discrete clinical analyzer. The concentration of drug determines the amount of conjugate that is bound to the drug antibody. The unbound conjugate catalyzes the oxidation of glucose-6-phosphate with the simultaneous reduction of NAD⁺ to NADH more rapidly than does the bound conjugate. The rate of increasing absorbance at 340nm due to the increase of NADH is related to drug concentration by means of a calibration curve or mathematical function. The within-run CV for this test is 4.7% at 8.7 µg/ml, 4.3% at 17.6 µg/ml, and 5.1% at 34.4 µg/ml.

Reference range:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Level</th>
<th>Trough Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>20-30 µg/ml</td>
<td>4-8 µg/ml</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5-10 µg/ml</td>
<td>0.5-2.0 µg/ml</td>
</tr>
</tbody>
</table>

Creatinine

The CREA method used on the DIMENSION™ clinical chemistry system is used for the quantitative determination of creatinine in serum, plasma, and urine. In the presence of a strong base such as NaOH, picrate reacts with creatinine to form a red chromophore. The rate of increasing absorbance at 510nm due to the formation of this chromophore is directly proportional to the creatinine concentration in the sample and is measured using a
bichromatic rate technique. The reference range for serum creatinine is 0.8–1.4 mg/dl.

**BUN**

The BUN enzyme method based on urease used on the DIMENSION™ clinical chemistry system is used to quantitate urea nitrogen in serum or plasma. The reference range for BUN is 7–20 mg/dl.

**Evaluation of Data**

Chi-square analysis of the data was performed to determine if there was a significant change in the ordering patterns of aminoglycoside serum levels following implementation of the guidelines. The data for chi-square consist of frequency counts or tallys rather than measurements in some sort of units. In this situation the null hypothesis was that the pattern for ordering aminoglycoside serum levels before and after implementation of the guidelines would be the same: \( H_0: \pi_B = \pi_A \). The alternate hypothesis was that the pattern for ordering serum levels before and after implementation of the guidelines would not be the same: \( H_0: \pi_B \neq \pi_A \).

The chi-square test was used to determine if the difference between the expected and observed values was significant. The distribution of expected frequencies was computed and compared with the observed values. The expected values were calculated by assuming that the same
proportion of serum levels would be ordered after implement-
tation of the guidelines as before.

If large differences exist across categories, a large chi-square value would be computed, and the null hypothesis would be rejected. If the observed frequencies are quite close to the expected values across categories, a small chi-square value would be computed and the null hypothesis would not be rejected. Chi-square was computed using the following equation:

\[ \chi^2 = n \frac{([ad-bc] - n/2)^2}{(a+b)(c+d)(a+c)(b+d)} \]

<table>
<thead>
<tr>
<th></th>
<th>OBSERVED</th>
<th>EXPECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRE</th>
<th>POST</th>
<th>TOTALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>a+c</td>
<td>b+d</td>
<td>n</td>
</tr>
</tbody>
</table>

\( a = \) number of serum levels ordered correctly (PRE-guidelines)

\( b = \) number of serum levels ordered correctly (POST-guidelines)

\( c = \) number of serum levels ordered incorrectly (PRE-guidelines)

\( d = \) number of serum levels ordered incorrectly (POST-guidelines)

\( a+c = \) total number of serum levels (PRE-guidelines)
\[ b + d = \text{total number of serum levels (POST-guidelines)} \]
\[ n = \text{total number of serum levels (PRE and POST)} \]

A chi-square table was consulted to determine the decision point for rejection of the null hypothesis. It tabulates various values of the chi-square distribution for different degrees of freedom (df). There was a 5% chance of rejecting a true null hypothesis by using the 0.05 significance level.

The following steps\textsuperscript{35} were followed:

1. \( H_0 \): there will be no difference in the pattern of ordering serum levels before and after implementation of the guidelines
2. \( H_a \): there will be a difference in the pattern of ordering serum levels after implementation of the guidelines
3. Using 0.05 significance level and 1 df: \( \chi^2 = 3.84 \)
   If the calculated \( \chi^2 \) is >3.84, reject \( H_0 \)
   If the calculated \( \chi^2 \) is <3.84, do not reject \( H_0 \)
RESULTS

Data collected from the charts of patients receiving aminoglycoside therapy were evaluated to assess the effect of implementation of the guidelines and laboratory-ordering worksheet on solving the perceived problems.

Guidelines

The patients who met each of the guideline criteria are presented in Table 1. Many patients fit more than one criterion for monitoring. The criteria most often met by patients in both the pre- and postguideline implementation groups were (1) therapy >8 days: 30% and 46%; (2) age >60 years with therapy >3 days: 32% and 36%; (3) ICU status: 38% and 34%; (4) serum creatinine >1.2 mg/dl: 24% and 22%; and (5) cystic fibrosis: 14% and 24%. Patients fitting additional guidelines of cumulative therapy >10 days in three months, liver disease, other nephrotoxic drugs and congestive heart failure were each <10%.

Hospital service and specific drugs. Patients within and without the guidelines both pre- and post-implementation are presented in Table 2. The medical service was represented by 84 (58%) patients; 42 (28%) were surgical patients and 20 (14%) were pediatrics. The number of pediatric patients nearly doubled in the POST group due to
Table 1

Patients Meeting Guideline Criteria for Serum Monitoring

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy $\geq$ 8 days</td>
<td>15 (30%)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Age $\geq$ 60 years, therapy $\geq$ 3 days</td>
<td>16 (32%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>ICU status</td>
<td>19 (38%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>$\geq$ 10 days cumulative in 3 months</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Serum creatinine $&gt;1.2$ mg/dl</td>
<td>12 (24%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Other nephrotoxic drugs</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>7 (14%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
Table 2
Patients Within and Without the Guidelines for Monitoring Aminoglycoside

<table>
<thead>
<tr>
<th>Service</th>
<th>Pre-guidelines Within</th>
<th>Pre-guidelines Without</th>
<th>Post-guidelines Within</th>
<th>Post-guidelines Without</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>27</td>
<td>18</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Surgical</td>
<td>16</td>
<td>3</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>7</td>
<td>0</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Drug</td>
<td>Amikacin</td>
<td>18</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>19</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>11</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Amikacin, then gentamicin</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Amikacin, then tobramycin</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Amikacin, then gentamicin, then tobramycin</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
the winter months when more cystic fibrosis patients were being treated with aminoglycosides for pseudomonas pneumonia. Among these patients, 45 (31%) were treated with amikacin, 64 (44%) with gentamicin, 26 (18%) with tobramycin and 11 (7%) with a combination of aminoglycosides.

Serum aminoglycoside levels. In both groups, patients within the guidelines were treated three times longer and had four times as many serum levels performed as patients not fitting criteria for being monitored. The average number of serum levels per days of therapy in the PRE and POST groups were the same (1 serum level/2.4 days of therapy).

Six patients within the guidelines had no serum levels performed. The PRE group included the following patients: two Pediatrics, one CVU, one SICU and one who expired. The POST group had one Pediatric patient. Table 3 represents these data.

Serum creatinine levels. The guidelines indicated that serum creatinine levels should be monitored every three to four days during therapy with aminoglycosides. Services not in compliance with this criterion in the PRE group included Pediatrics (seven patients) and Surgery (two patients). The POST group included 12 Pediatric patients and 1 Medical patient.
### Table 3

Days of Therapy and Number of Serum Levels Within and Without the Guideline Criteria

<table>
<thead>
<tr>
<th></th>
<th>Preguidelines</th>
<th></th>
<th>Postguidelines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within</td>
<td>Without</td>
<td>Within</td>
<td>Without</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of days</td>
<td>9.4</td>
<td>3.6</td>
<td>12.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Range</td>
<td>2-39</td>
<td>1-8</td>
<td>4-31</td>
<td>2-7</td>
</tr>
<tr>
<td>Serum Drug Levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of levels</td>
<td>4.1</td>
<td>0.9</td>
<td>5.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Range</td>
<td>0-20</td>
<td>1-8</td>
<td>0-15</td>
<td>0-5</td>
</tr>
<tr>
<td>Number of patients with no levels</td>
<td>9</td>
<td>14</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Levels ordered correctly:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hours weekly</td>
<td>79</td>
<td>19</td>
<td>109</td>
<td>19</td>
</tr>
<tr>
<td>weekly</td>
<td>9</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Levels ordered incorrectly:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hours weekly</td>
<td>22</td>
<td>13</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>weekly</td>
<td>13</td>
<td>3</td>
<td>16</td>
<td>-</td>
</tr>
</tbody>
</table>
Aminoglycoside-associated nephrotoxicity. Of the patients, 4 of 50 (8%) in the PRE group and 7 of 50 (14%) in the POST group that were within the guidelines experienced an increase in their serum creatinine that could be associated with their drug therapy, consistent with most estimates of the frequency of aminoglycoside-associated nephrotoxicity which ranges between 8% and 26%. One patient in the PRE group who did not fit the guidelines criteria was in septic shock and had an increase in serum creatinine of 0.8 mg/dl which resolved within one day when the urine output improved (Table 4).

The four patients in the PRE group exhibited the following increases: (1) 0.9 mg/dl to 1.5 mg/dl, (2) 1.1 mg/dl to 3.9 mg/dl (3) 0.9 mg/dl to 1.5 mg/dl and (4) 2.0 mg/dl to 3.1 mg/dl. The seven patients in the POST group

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Preguidelines</th>
<th>Postguidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within</td>
<td>Without</td>
<td>Within</td>
</tr>
<tr>
<td>Patients with increase</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Patients with no increase</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>Patients not monitored</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>
exhibited the following increases: (1) 1.4 mg/dl to 2.2 mg/dl, (2) 0.6 mg/dl to 1.5 mg/dl, (3) 2.0 mg/dl to 2.6 mg/dl, (4) 1.0 mg/dl to 2.6 mg/dl, (5) 1.1 mg/dl to 2.3 mg/dl, (6) 1.2 mg/dl to 3.1 mg/dl and (7) 1.2 mg/dl to 3.4 mg/dl.

**Microbiology reports.** Microbiology reports confirmed that 20 patients (40%) in the PRE group and 25 patients (50%) in the POST group were treated with drugs to which the organisms were sensitive. Of the patients, 13 PRE (26%) and 8 POST (16%) were treated with aminoglycosides when gram positive and/or gram negative organisms were isolated but there were no sensitivities reported. The protocols followed by ARUP and the groupings of antimicrobial agents that should be considered for routine testing suggested by the National Committee for Clinical Laboratory Standards (NCCLS)\(^{36}\) are included in Appendix G and H. A retrospective study of the patients in each group indicated that in the PRE group, cultures were ordered for only three patients, two charts were missing or unavailable and eight patients had no sensitivities reported. A summary of those eight patients follows:

- 3 cultures had no pathogens
- 1 culture had \(<10,000\) colonies per milliliter of urine
- 2 cultures were Streptococcus, which is predictably susceptible to penicillin
- 1 culture had \(>4\) organisms
1 culture had *Staphylococcus aureus* and sensitivities were performed with drugs recommended by NCCLS. In the POST group, culture was ordered for only one patient, three charts were missing or unavailable and three patients had no sensitivities reported. A summary of those three patients follows:

- 1 culture had <10,000 colonies per milliliter of urine
- 1 culture had no pathogens
- 1 had no sensitivities ordered

Reportedly, the Southwest Oncology Group suggests that amikacin be used prophylactically and six patients (12%) PRE and seven patients (14%) POST with diagnoses of leukemia were treated when cultures were negative or not done. An additional 11 patients (22%) PRE and 5 patients (10%) POST were treated on other services when cultures were negative or not done.

When sensitivities indicated that the organism was sensitive to both amikacin and gentamicin, amikacin was used 35% (6/17) in the PRE group and 26% (6/23) in the POST group. In both groups tobramycin was used on two patients whose organisms were sensitive to gentamicin. Tobramycin was used routinely for cystic fibrosis patients.

**Laboratory-ordering worksheet.** The laboratory ordering worksheet was sent to the laboratory with 194/331 serum levels ordered (59%). Of the worksheets sent, 148/194 (76%) were filled out correctly. Data regarding the compliance of each service are included in Table 5.
Table 5
Compliance in the Use of Laboratory-ordering Worksheets

<table>
<thead>
<tr>
<th>Hospital Service</th>
<th>Worksheets</th>
<th></th>
<th>Completed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sent</td>
<td>Not Sent</td>
<td>Correctly</td>
<td>Incorrectly</td>
</tr>
<tr>
<td>CVU</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>SICU</td>
<td>25</td>
<td>26</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>3N</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>CCU</td>
<td>24</td>
<td>25</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>4N</td>
<td>27</td>
<td>6</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>5N</td>
<td>38</td>
<td>22</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>5S</td>
<td>39</td>
<td>12</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>6N</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>6S</td>
<td>22</td>
<td>25</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>TOTALS</td>
<td>194</td>
<td>137</td>
<td>148</td>
<td>46</td>
</tr>
</tbody>
</table>
Information lacking on the 24% done incorrectly included:

Number of peak levels:
1. time last infusion was completed 9
2. date and time specimens were drawn 7
3. identification of phlebotomist 8

Number of trough levels:
1. time last infusion was completed 8
2. date and time specimen was drawn 6
3. identification of phlebotomist 9

Item 2 in trough levels and item 4 in peak levels, which are signed when the laboratory is notified, were incomplete on 95 (46 trough and 49 peak) worksheets.

Problems which were similar to the ones reported in 1985 were observed. Six of these were evaluated using the laboratory-ordering worksheets.

1. Patient A was receiving gentamicin but had amikacin serum levels performed. Although the worksheet indicated gentamicin, the request form sent by the service unit personnel requested amikacin levels.

2. Patient B had been treated with amikacin for four days with four previous serum levels being within the therapeutic range. The next trough level was <0.2 mg/dl just 24 hours after a normal trough. No worksheet was submitted, but a check with the nursing service indicated the sample presumably had been drawn by a nurse from the wrong patient. Two subsequent trough levels in the next five days were within range.
3. Patient C had peak and trough levels both reported as troughs. Although a worksheet was completed correctly, lab request slips accompanying the samples both ordered troughs.

4 & 5. Patients D and E had extremely high peak levels (amikacin 150 mg/dl and gentamicin 39 mg/dl). Intravenous contamination was a possibility, although worksheets were not completed, making identification of the phlebotomist impossible.

6. Patient F receiving gentamicin was reported to have a trough of 2.4 mg/dl H and a peak of 4.8 mg/dl L. The times on the tubes and requests indicated that the trough had been drawn 10 minutes after the peak. There was no worksheet submitted to use in determining the correct times.

Cystic fibrosis patients. Seven patients with a diagnosis of cystic fibrosis were studied in the PRE group. They were all treated with tobramycin for an average of 10.6 days. Two patients had no serum drug levels performed and the other five patients had an average of two levels. Only one patient had serum creatinine levels performed every three to four days.

The POST group included 12 patients, all treated with tobramycin for an average of 12 days each. Of these, 1 patient had no serum drug levels performed while the other 11 patients had an average of 3.5 levels. A total of 38 (55%) of the serum drug levels was ordered as the guide-
lines suggested. None of the 12 patients in the POST group had serum creatinines performed as suggested by the guidelines (every three to four days), although 10 of the patients had serum creatinines performed at least once (Table 6).

Analysis of Data

The chi-square test was utilized to determine if there were significant changes in the ordering patterns of serum levels after implementation of the guidelines. The results of the chi-square tests were as follows:

Analysis of serum levels ordered at 72 hours:

number of serum levels ordered correctly (PRE) = 79
number of serum levels ordered correctly (POST) = 109
number of serum levels ordered incorrectly (PRE) = 22
number of serum levels ordered incorrectly (POST) = 7

\[ \chi^2 = 11.56 \text{ which is } >3.84, \therefore \text{ reject } H_0. \]

There was a significant improvement in the number of serum levels ordered correctly at 72 hours following the implementation of the guidelines.

Analysis of serum levels ordered weekly:

number of serum levels ordered correctly (PRE) = 9
number of serum levels ordered correctly (POST) = 5
number of serum levels ordered incorrectly (PRE) = 13
number of serum levels ordered incorrectly (POST) = 16

\[ \chi^2 = 1.430 \text{ which is } <3.84, \therefore \text{ do not reject } H_0. \]

There was not a significant difference in the number of serum levels ordered weekly.
Table 6
Data for Cystic Fibrosis Patients

<table>
<thead>
<tr>
<th></th>
<th>Preguidelines</th>
<th>Postguidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of days</td>
<td>10.6</td>
<td>12</td>
</tr>
<tr>
<td>Range</td>
<td>5-23</td>
<td>5-28</td>
</tr>
<tr>
<td><strong>Serum Drug Levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of levels</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Range</td>
<td>0-6</td>
<td>0-8</td>
</tr>
<tr>
<td>Number of patients with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no levels performed</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Number of levels ordered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>correctly:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hours</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>weekly</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Number of levels ordered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>incorrectly:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hours</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>weekly</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients monitored every</td>
<td></td>
<td></td>
</tr>
<tr>
<td>three to four days</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patients not monitored every</td>
<td></td>
<td></td>
</tr>
<tr>
<td>three to four days</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>
DISCUSSION AND RECOMMENDATIONS

Group participation in developing solutions to the problems reported by the pharmacy resident in 1985 was facilitated by the formation of an aminoglycoside review committee. To enable the acceptance of changes, all of the departments involved had influence and control over the final solution.

There was significantly greater compliance POST-implementation of the guidelines in regard to levels being run within 72 hours of initiation of treatment or changes in parameters. Weekly serum levels were being ordered incorrectly prior to implementation of the guidelines as well as after. It is apparent that guidelines are necessary inasmuch as patients who meet those criteria are treated longer and require more serum levels.

The incidence of aminoglycoside-associated nephrotoxicity (8% PRE and 14% POST) is compatible with previously reported rates. Of the 11 patients with elevated serum creatinine levels in all groups, 5 of them were terminal, 2 had congestive heart failure and there was 1 each diagnosed with liver disease, pancreatitis, pneumonia and cholelithiasis. Often patients receiving aminoglycoside therapy are seriously ill. Of the patients who were terminal, nephrotoxicity may well have been related to organ failure.
The cost of 500 mg of amikacin is about $30.00, 80 mg of gentamicin about $9, and 80 mg of tobramycin, about $18. The cost of a dose of amikacin ($0.45/mg/kg) is nearly twice the cost of a dose of gentamicin ($0.023 mg/kg). Cost savings for the patients could be realized if patients were treated with gentamicin instead of amikacin when an organism is sensitive to both. Additional cost savings for the patient would result if duplicate serum levels being ordered due to questionable results could be eliminated. This is only accomplished, however, when a follow-up is made to determine the source of the problem. On several occasions the term "laboratory error" was recorded on the patient's chart without further documentation. The laboratory investigates all such critical incidents when reported.

The laboratory-ordering worksheet was effective in resolving problems when correctly completed. The service personnel appear reluctant to complete the lines that refer to notification of the laboratory. Because this information is not critical to any calculation, it is suggested that those items be removed from the worksheet. The worksheets should also be better correlated by the laboratory with the specimens and laboratory request forms to prevent incorrect drugs being tested and results being reported as both peaks and troughs.

Education of all areas involved was critical in effecting change. Education needs to be ongoing, as new
staff have obviously been added in the past year. Reminders should appear in all of the newsletters including the House Staff Newsletter and inservice training should be repeated for nurses, phlebotomists and involved laboratory staff. Follow-up by Quality Assurance will be essential if there is to be continued compliance with the guidelines.

Evidence presented documents the positive impact of having interaction with all health professionals involved when attempting to resolve problems. Considerable effort was expended in writing and revising the guidelines to provide quality care for the patients. It was essential that the guidelines not be too restrictive, which would have led to increased costs for the patient if too many levels had been recommended. The number of serum levels recommended appears to be reasonable in monitoring the patients for the achievement of therapeutic levels and prevention of nephrotoxicity.

Solutions to the problems associated with aminoglycosides will be useful in resolving problems with other drugs and patient care problems involving multidisciplinary areas of the hospital. Careful evaluation of the problems by all concerned and a rational approach to finding solutions will help assure the quality of patient care.

Based upon the findings of this study, the following recommendations are offered:
Laboratory

1. Revise the laboratory-ordering worksheet into two forms, one for peak levels and another for trough levels, because the samples arrive in the laboratory at different times.

2. Perform the serum levels only when the worksheets accompany the samples.

3. Add the "infusion completion time" to the report so that the physician/pharmacy will be provided with complete information.

4. Be especially observant when reviewing laboratory reports to notice when two troughs or two peaks are being reported.

5. Use the laboratory-ordering worksheets for troubleshooting and resolution of problems.

6. Conduct additional inservices for phlebotomy and chemistry.

7. Provide an update and review in the laboratory newsletter.

Nursing

1. Provide nursing staff with additional inservice training in the use of the laboratory-ordering worksheet and guidelines.

2. Provide an update and review in the nursing newsletter.

3. Report any critical incidents to the laboratory for follow-up.
Quality Assurance

1. Follow-up on the aminoglycoside being used for its appropriateness
2. Review guidelines and procedures in newsletter

Aminoglycoside Review Committee

1. Review results of this study
2. Reconsider the appropriateness of including cystic fibrosis patients in the guidelines
Aminoglycoside serum level monitoring is performed for three major applications: (1) serum levels are not reliably predictable from the drug dose and dosing interval, (2) a documented relationship exists between therapeutic level and efficacy, (3) a documented relationship exists between some combination of drug dose and duration of therapy and toxicity. All patients receiving aminoglycosides should have serum creatinines monitored every three to four (3-4) days during therapy. In addition, drug peak and trough levels are indicated in the following situations:

1. Therapy anticipated to continue $\geq 8$ days

2. Therapy anticipated to last $< 8$ days if one or more of the following risk factors is present:
   a. Age $\geq 60$ years if therapy is anticipated to continue $\geq 3$ days
   b. ICU status with suspected or proven bacteremia
   c. Cumulative days of aminoglycoside therapy within the preceding three months
d. Serum creatinine $>1.2$ mg/dl or creatinine clearance $<70$ ml/min in adults. Note that in pediatric patients the serum creatinine varies with age, thus a specific definition of abnormal renal function cannot be quoted. This must be taken into account when determining the need for aminoglycoside monitoring in the pediatric population.

e. Significant liver disease

f. Shock or severe intravascular volume depletion

g. Concomitant therapy with other potentially nephrotoxic drugs, such as:
   (1) Loop diuretics (e.g., furosemide, bumetanide)
   (2) Nonsteroidal anti-inflammatory drugs
   (3) Amphotericin B
   (4) Cyclosporin A

h. Cystic fibrosis

i. Refractory hypokalemia

j. Other clinical situations which may imply decreased renal function or altered volume of distribution, e.g., moderate to severe CHF, morbid obesity, severe burns

If monitoring of drug levels is indicated, initial values should be obtained within the first 72 hours of therapy. If no dosage adjustments are required and major...
physiologic parameters remain unchanged, levels may be followed on a weekly basis.

The peak serum level should be drawn approximately 30 minutes after the completion of a 30- to 60-minute intravenous infusion of drug. The trough level is usually drawn within 30 minutes of the next drug infusion. These two levels may be calculated, however, from any two levels drawn after the first 30 minutes so long as the time of drug infusion and blood draws are known. The following are serum levels for commonly used aminoglycosides as defined by the ARUP laboratories.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Therapeutic Level</th>
<th>Trough Level (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>5 - 10</td>
<td>0 - 2.0</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>4 - 10</td>
<td>0 - 2.0</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20 - 30</td>
<td>4 - 8</td>
</tr>
</tbody>
</table>

Consultation about any aspect of aminoglycoside dosing or monitoring can be obtained on a 24-hour basis by calling the Drug Information Center at 581-2073.
APPENDIX B

GUIDELINES FOR AMINOGLYCOSIDE USE AND MONITORING IN NEONATES

Neonates: Infants who are less than or equal to 44 weeks postconceptual age.

General Dosage Guidelines: Derived from consultants and the limited literature in neonates.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosages* (mg/kg/dose)</th>
<th>Serum Peak Conc. (µg/ml)</th>
<th>Serum Trough Conc. (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>2.5 - 3.5</td>
<td>5 - 8</td>
<td>0.5 - 2</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2.5 - 3.5</td>
<td>5 - 8</td>
<td>0.5 - 2</td>
</tr>
<tr>
<td>Amikacin</td>
<td>7.5 - 10</td>
<td>15 - 20</td>
<td>3 - 5</td>
</tr>
</tbody>
</table>

*Dosages: To achieve adequate peak aminoglycoside concentrations in extremely premature neonates with larger volumes of distribution, the individual dosages may have to be increased as suggested by Lugo et al. (J Perinatol 6:337-341, 1986) (e.g., for gentamicin to 3.5 mg/kg/dose).

Initial Dosing Intervals: During the first few days after birth, aminoglycoside dosing intervals in neonates should be adjusted according to postconceptual age and should generally follow the recommendations of Zarowitz et al. (Dev Pharmacol Ther 5:68-75, 1982):

- less than 28 weeks - one dose q 24 hours
- 28-34 weeks - one dose q 18 hours
greater than 34 weeks - one dose q 12 hours for first 7 days, then q 8 hours

Later Dosing Intervals: May be adjusted to Glomerular Filtration Rate (GFR) as indicated by the time required for trough concentrations to decrease below the lower limits listed above. Shorter dosing intervals may not be needed for 4 weeks in the extremely premature neonates.

Renal Function: Aminoglycoside elimination is closely related to GFR. Although unproved, aminoglycosides may produce renal toxicity in neonates. Serum creatinine should be measured before treatment and every 3-4 days during treatment. An increase of creatinine greater than or equal to 0.3 mg/dl in a neonate is abnormal.

Sample Timing: Peak concentrations should be measured 30-60 minutes following the end of the infusion of an intravenous dose or 1 hour after administration of an intramuscular dose. Trough concentrations should be measured 1-60 minutes before administration of a dose.

Note Times of End of Dose and Sample Collections to Calculate a Half-life.

Early Monitoring: Peak concentration of aminoglycoside should be monitored after the second dose and a trough concentration before the third dose in neonates with:

1. Evidence of renal insufficiency
2. Strong clinical evidence of infection or positive cultures of significant body fluids
Later Monitoring: Peak and trough concentrations of aminoglycosides should be monitored in neonates who:

1. Receive aminoglycoside therapy for longer than 3 days (monitor every 3-5 days)
2. Lose greater than 15% of birth weight (D16), or attain serum Na greater than meq/L

No Monitoring: Aminoglycoside concentrations do not need to be monitored in neonates receiving antibiotics for three days or less without the indications listed above.

Action: Doses and dosing intervals should be adjusted to achieve effective peak concentrations and avoid accumulating concentrations if the dosing interval is too short. After dose adjustments, additional monitoring is indicated to insure attainment of the desired therapeutic goals.
APPENDIX C

ARUP WORKSHEET

ADDRESSOGRAPH

ARUP

AMINOCYCLOSIDE SERUM LEVEL WORKSHEET
(To be completed by nursing personnel/lab)

Requesting Physician ____________________ Patient Service ___________

Drug to be Determined ____________________________________________

Tests Requested:

TROUGH Level Only
(Note: Should be drawn 5-90 minutes before next drug infusion is to begin).

PEAK Level Only
(Note: Should be drawn at least 30 minutes following the completion of the drug infusion).

TROUGH and PEAK Levels
(Note: Worksheet remains on the bedside clipboard until the peak level is collected.

TROUGH LEVELS:
1. Last infusion completed ________R.N.____ Date/Time

2. Call lab (X2430) to schedule specimen collection. Complete test request process. Completed by ________ (PCU Staff).

3. Specimen drawn ________Date/Time____ by ________Name____ (phlebotomist).

PEAK LEVELS:
1. Infusion started ________Date/Time____ by ________Name____ (R.N.).

2. Infusion completed ________Date/Time____ noted by ________Name____ (R.N.).

3. Call lab (X2430) to schedule draw. Complete test request process. Completed by ________ (PCU Staff).

4. Specimen drawn ________Date/Time____ by ________Name____ (phlebotomist).

Lab Personnel Only: Comment date and time when result entering.
APPENDIX D

AMINOGLYCOSIDE DOSING CHART

1. Select Loading Dose in mg/kg [IDEAL WEIGHT] to provide peak serum levels in range listed below for desired aminoglycoside.

<table>
<thead>
<tr>
<th>AMINOGLYCOSIDE</th>
<th>USUAL LOADING DOSES</th>
<th>EXPECTED PEAK SERUM LEVELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>1.5 to 2.0 mg/kg</td>
<td>4 to 10 µg/ml</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>5.0 to 7.5 mg/kg</td>
<td>15 to 30 µg/ml</td>
</tr>
<tr>
<td>Kanamycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient's corrected creatinine clearance.

<table>
<thead>
<tr>
<th>PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clocker (mL/min)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>17</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

*Reprinted by permission from Annals of Internal Medicine
Background
Infections commonly treated with aminoglycoside therapy include urinary tract infections, bacteremia, pneumonia, peritonitis, osteomyelitis, infected burns, meningitis, and pelvic infections. As bactericidal antimicrobial agents, aminoglycosides induce cell death by eliciting the formation of defective proteins in gram negative bacteria. These drugs which are primarily protein-bound in vivo, are distributed principally in extracellular fluid. However, aminoglycosides have a marked affinity for the renal cortex and may accumulate in these tissues at levels 50-100 times greater than the plasma concentrations. Several mechanisms have been proposed to explain their overall toxicity. Nephrotoxicity, the most frequent complication is seen in 2-10 percent of patients on aminoglycoside therapy.

Recent studies have suggested that inappropriate utilization of aminoglycoside testing may be contributing to less than optimum patient care and may also be increasing health care costs. An interdisciplinary committee was formed to review the issues.

The objective of this quality assurance effort is to optimize the utilization of aminoglycoside testing for patient care. Overutilization of therapeutic drug monitoring adds cost to patient health care and must be controlled. Furthermore, by following an appropriate patient monitoring protocol, toxic drug levels can generally be avoided and the cost of patient care reduced.

It is hoped that this quality assurance effort might establish a pattern for the critical review of utilization patterns for other laboratory tests, an increasingly important issue confronting medical educators and providers.

Guidelines
Guidelines for aminoglycoside utilization have been established to optimize patient care. Implementation of these guidelines requires the cooperation of many health care professionals. Already this quality assurance effort has included representatives from the Departments of Medicine, Pathology, Pharmacy, Pediatrics, Obstetrics, and Nursing at the University of Utah School of Medicine, and ARUP. The "Guidelines for Aminoglycoside Monitoring" as approved by the clinical departments are attached.

In addition, a specimen collection worksheet has been designed to assist in the appropriate specimen collections for peak and/or trough levels:

Specimen Collection Worksheet:

[Table containing various specimen collection instructions and dates]
Laboratory Testing
Methods available for analysis of aminoglycosides in serum or plasma include chromatography, radioimmunoassay, fluorescence polarization, and enzyme immunoassay techniques. Aminoglycoside assays are performed at ARUP by fluorescence polarization and/or enzyme immunoassay techniques.

References

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Master's Degree Student

Edited by: Harry Hill, M.D.
DeVon Hale, M.D.

Attachments approved by: The Aminoglycoside Committee at the University of Utah Medical Center
GUIDELINES FOR MONITORING AMINOGLYCOSIDE THERAPY APPROVED by R. Jane Lau, M.D., Chairman, Aminoglycoside Monitoring Subcommittee and Linda Tyler, Pharm.D.

A subcommittee of the Pharmacy and Therapeutics Committee has been working for the last year to develop guidelines for monitoring aminoglycoside therapy. This subcommittee was formed because there was frequent inappropriate use of aminoglycoside levels as a monitoring tool. Both underutilization and overutilization were identified as problems. Representatives from many departments were included in this process, including representatives from Nephrology, Infectious Disease, Obstetrics and Gynecology, Pediatrics, Pathology, ARUP, Nursing, Quality Assurance, and Pharmacy.

Keep in mind that these are intended as GUIDELINES. The P & T Committee is aware that there will be instances when levels are indicated that are not covered by these guidelines. Likewise, aminoglycoside levels should not be automatically ordered just because the patient is receiving an aminoglycoside. Some thought should be given to the reason the serum concentration determination is being requested. These recommendations reflect what the subcommittee believed were the minimum standards for monitoring for toxicity and efficacy. There are two sets of guidelines: Guidelines for neonates are available separately on those units that care for neonatal patients. The following guidelines are for all other patients.

GUIDELINES FOR AMINOGLYCOSIDE MONITORING FOR PATIENTS GREATER THAN 44 WEEKS POSTCONCEPTUAL AGE

Careful monitoring of serum concentrations in patients receiving aminoglycoside antibiotics is necessary because: 1. For some patients it is impossible to predict the serum levels of the drug even when a nomogram is used to select the dose and dosing interval. 2. There is a documented relationship between therapeutic serum concentrations and clinical response. 3. There is a documented relationship between the combination of drug dose and duration of therapy and toxicity.

Obviously, each of these goals suggests a different pattern and frequency of monitoring. The following guidelines represent minimal monitoring criteria to satisfy these goals understanding that individual clinical circumstances may suggest much more frequent or intensive surveillance. Since aminoglycoside elimination is closely related to the GFR, all patients receiving these drugs should have a baseline serum creatinine drawn with values repeated every three to four days for the duration of therapy.

In addition, aminoglycoside peak and trough levels are indicated in the following clinical settings:

1. Therapy is anticipated to continue for 8 days or longer.
2. Therapy is anticipated to last less than 8 days but one of the following risk factors is present:
   a. Age greater than 60 years and therapy is anticipated to last greater than 3 days.
   b. Patient is in the ICU with proven or suspected bacteremia.
   c. Patient has received greater than 10 cumulative days of aminoglycoside therapy within the preceding 3 months.
   d. Serum creatinine greater than 1.2 mg/dl or creatinine clearance less than 70 ml/min in adults. Note, in pediatric patients the serum creatinine varies with age, thus a specific definition of abnormal renal function cannot be quoted. This must be taken into account when determining the need for aminoglycoside monitoring in the pediatric population.
   e. Significant liver disease.
   f. Shock or severe intravascular volume depletion.
   g. Concomitant therapy with other potentially nephrotoxic drugs such as:
      - Loop diuretics e.g. furosemide, bumetanide
      - Nonsteroidal antiinflammatory drugs
      - Amphotericin B
      - Cyclosporin A
      - Cystic fibrosis patients
      - Refractory hypokalemia
      - Other clinical situations which may imply decreased renal perfusion or altered volume of distribution, e.g. moderate to severe CHF, morbid obesity, severe burns.

If monitoring of drug levels in indicated, the initial values should be obtained within the first 72 hours of
therapy. If no dosage adjustments are required and major physiologic parameters remain unchanged, levels may be followed on a weekly basis. Many clinical situations may benefit from more frequent monitoring.

Aminoglycoside antibiotics follow first order pharmacokinetics which means that, after an initial distribution phase, the elimination phase follows a straight line when the log of the drug concentration is plotted against time. The peak serum level is defined as that level drawn at the end of the distribution phase or approximately 30 minutes after the completion of a 30 to 60 minute infusion. The trough level is the lowest level of drug reached before the next infusion. Practically, this level is usually drawn within 30 minutes of the subsequent dose. The existence of first order pharmacokinetics allows the calculation of peak and trough levels from any 2 points on the elimination curve, provided the exact timing of both drug infusion and blood draw is known. The ARUP laboratory has defined the "normal" serum levels for commonly used aminoglycoside antibiotics as:

**Gentamicin:** peak 5 - 10 mcg/ml  
trough 0.5 - 2.0 mcg/ml  
**Tobramycin:** peak 5 - 10 mcg/ml  
trough 0.3 - 2.0 mcg/ml  
**Amikacin:** peak 20 - 30 mcg/ml  
trough 4 - 8 mcg/ml

ARUP laboratory reporting time for aminoglycoside levels is 24 hours for routine tests, 60 - 90 minutes for priority tests, and 30 minutes for those designated stat. If a clinical situation mandates an urgent level, the stat or priority designation should be used. For example, if a trough level is needed to determine the next aminoglycoside dose, this may be ordered as a stat or priority test and drawn up to 90 minutes prior to the next scheduled dose. Aminoglycoside serum levels may be ordered separately as peak or trough levels or randomly so long as the necessary times of drug infusion and blood draw are recorded.

Consultation about aminoglycoside dosing or monitoring can be obtained on a 24 hour basis by calling the Drug Information Center at 581-2073.

### NEW HOURS FOR OUTPATIENT PHARMACY

The Outpatient Pharmacy has extended its hours to better meet the needs of the patients and staff of University Hospital. The new hours are:

- **Monday - Friday:** 8 am to 6:30 pm  
- **Saturday:** 8 am to 4:30 pm  
- **Sunday:** 8 am to 1 pm

### FORMULARY ADMISSIONS

The following drugs were admitted to the Formulary at the August meeting of the Pharmacy and Therapeutics Committee. The AHFS numbers refer to the pharmacological classifications used in the American Hospital Formulary Service Drug Information, available on each patient care unit and the pharmacy satellites.

- **Anusol HC Cream** will be stocked in addition to the Anusol HC Suppositories.
- **Calcium carbonate and calcium citrate** (AHFS 56:04 Antacids and AHFS 40:12 Replacement solutions) were both added to provide renal patients taking calcium products to treat hyperphosphatemia a choice of products to take. In addition to the calcium carbonate tablets 650 mg and suspension (Tiritralac) that is currently stocked, the Pharmacy will also stock Cal Carb HD (calcium carbonate powder) and Citracal (calcium citrate tablets 650 mg).
- **Demeclocycline** (Declomycin - Lederle, AHFS 8:12.24 Tetracycline) is useful for some bone scanning techniques and in the treatment of SIADH. It is available in 150 mg tablets. This is considerably more expensive than other tetracyclines and should only be used for these specific uses.
- **Diltiazem** (Cardizem - Marion, AHFS 24:04 Cardiac Drugs) is now available in 90 mg and 120 mg tablets. These 2 strengths will be stocked in addition to the 30 mg and 60 mg tablets.
- **Encainide** (Enkaid - Bristol, AHFS 24:04 Cardiac Drugs) is a new Type I C antiarrhythmic agent available in 25 mg, 35 mg and 50 mg capsules.
- **Etoposide** (VePesid - Bristol Myers, AHFS 10:00 Antineoplastic agents) is now available in an oral dosage form, 50 mg capsules.
- **Oxytetracycline with Polymyxin B Ophthalmic Ointment** (Terramycin with Polymyxin B - Rorer, AHFS 52:04.04 Ophthalmic anti-infectives) was added as an alternative to aminoglycoside ointments for the management of conjunctivitis. It is available in 3.75 G tubes.
- **Praziquantel** (Biltricide - Miles, AHFS 8:08 Anthelmintics) is labeled for use in treating schistosomiasis. There are some clinical studies supporting its use in the management of cerebral cisticercosis. It is available in 600 mg scored tablets.

### CHANGES IN FORMULARY RESTRICTIONS

Maprotiline is no longer restricted to Psychiatry.

Committee Capsules is published monthly by the Department of Pharmacy Services under the auspices of the Pharmacy and Therapeutics Committee; Linda S. Tyler, Pharm.D. and Roger R. Williams, M.D., editors. For more information on any item presented in Committee Capsules, contact the Drug Information Service, 581-2073. Copyright 1987 Department of Pharmacy Services, University of Utah Hospital, Salt Lake City, Utah.
APPENDIX G

ASSOCIATED AND REGIONAL UNIVERSITY PATHOLOGISTS, INC.

CLINICAL MICROBIOLOGY LABORATORY

PROCEDURE MANUAL, SECTION III

Urine Culture

(See separate protocol for Rehab Urines, and Autobac Urine Screen)

I. Rejection Criteria

A. Any delay in transport greater than 2 hours at RT.
B. Any delay in transport greater than 24 hours at 4°C.
C. Multiple specimens in 24-hour period.
D. Foley catheter tips.
E. Urines collected from catheter bags (if cath urine arrives in greater than 5 cc quantity, contact floor to verify collection method).
F. Nonsuprapubic aspirates requested for anaerobe culture.

II. Gram Stain

A. Perform on unspun specimen.

1. Perform on all urines requesting a gram stain.
2. Perform on all urines referred from urinalysis due to presence of WBC.
3. Perform on all urines indicating a diagnosis of FUO.

B. Report of gram stain

1. Report organisms per oil immersion field (average of 10 fields).
2. Report must be telephoned to physician or floor.
3. If stain reveals possible anaerobic organisms, notify physician and suggest
collection of a suprapubic aspirate for anaerobe culture.

III. Culture

A. Materials

1. Columbia sheep blood agar plate (SB).
2. MacConkey agar plate (Mac).
3. Calibrated 0.001 ml platinum loop.
4. Calibrated 0.1 ml pipetting device with sterile tip.

B. Plating procedure

1. Mix urine well.
2. Use a sterile loop (0.001) to obtain urine. (Note: loop must be in a vertical position when obtaining sample.)
3. Streak the SB plate as illustrated below:

   Begin streak in the middle of the plate. Spread urine for optimum growth of isolated colonies.

4. Repeat the procedure for the MacConkey plate.
5. On all suprapubic urines or ureteric urines (obtained during nephrostomy), include 0.1 ml SB. Streak in the manner illustrated above, labeling the plate to indicate the amount of inoculum.

IV. Colony Count Determination

A. On plates which show growth, estimate the number of colonies and multiply by 1000 to determine the number of colonies per milliliter of urine (the
number of colonies counted is the number of colonies per 0.001 ml urine).

1. When organisms grow on more than one plate, average the colony counts.
2. Colony counts are made to the nearest 10 (with the exception of counts between 1 and 10). For example:

   1-10 colonies: Report actual number present x 1000.
   10-15 colonies: Report as 10,000 cfu/ml.
   16-25 colonies: Report as 20,000 cfu/ml, etc.
   more than 100 colonies: Report as >100,000 cfu/ml.

3. Count the number of colonies on the 0.1 ml SB and multiply by 10 to obtain the number of colonies per milliliter.

V. Culture Work-up

A. Suprapubic or ureteric urines

1. Sterile cultures
   a. Send preliminary report as "No growth after x hours," after a minimum of 12 hours incubation. Reincubate SB (0.1 and 0.0001) plates for an additional day. Report as "No growth after 2 days."

2. Cultures with growth
   a. Work up all isolates.
   b. Perform sensitivities, if requested.

B. Catheter, antibiotic or renal transplant urines

1. Sterile cultures
   a. Send preliminary report as "No growth after x hours," with a minimum of 12 hours incubation. Reincubate SB (0.001) plate for an additional day. Report as "No growth after 2 days."

2. Cultures with growth
   a. Less than 10,000 cfu/ml: gross identification only (example: 8000
cfu/ml lactose fermenting gram negative rod).

b. Greater than 10,000 cfu/ml: complete identification if three or less organisms present. Sensitivities if requested.

c. Four or more organisms: gross identification only. Notify floor requesting a repeat specimen, hold plates on bench with a three day outdate, send out final report.

Flow Chart
Catheter or Antibiotic Urines

<table>
<thead>
<tr>
<th>Sterile cultures</th>
<th>&lt;10,000 cfu/ml</th>
<th>&gt;10,000 cfu/ml</th>
<th>4 or more organisms</th>
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<tbody>
<tr>
<td>Preliminary report on Day 1</td>
<td>Gross id only</td>
<td>Complete id</td>
<td>Gross id only</td>
</tr>
<tr>
<td>Final report on Day 2</td>
<td></td>
<td>Sens if requested</td>
<td>Request repeat culture</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hold plates 3 days</td>
</tr>
</tbody>
</table>

C. Clean Catch Urines

1. Sterile cultures

a. If plates have incubated 18 hours or more send final report as "No growth after x hours."

b. If plates have incubated less than 18 hours, reincubate SB (0.001) for an additional day. Send preliminary report as "No growth after x hours," with a minimum of 12 hours incubation. Report as "No growth after 2 days."

2. Cultures with growth

a. Less than 10,000 cfu/ml: gross identification only (example: 7000 cfu/ml gamma hemolytic Strep).

b. 10,000-50,000 cfu/ml: complete identification if 3 or less organisms present. No sensitivities performed.
c. Greater than 50,000 cfu/ml: complete identification if 3 or less organisms present. Sensitivities if requested.

d. Four or more organisms: gross identification only. Notify floor, request a repeat specimen, hold plates on the bench with a three-day outdate, send out final report.

Flow Chart

Clean Catch Urines

<table>
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<tr>
<th>Sterile</th>
<th>&lt;10,000 cfu/ml</th>
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<th>&gt;50,000 cfu/ml</th>
<th>4 or more organisms</th>
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<td>Preliminary report (12 to 18 hours incubation)</td>
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<tr>
<td>Final report minimum 18 hours incubation</td>
<td>No sensitivities</td>
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<td>Sens if requested</td>
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<tr>
<td></td>
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<td>Hold plates 3 days</td>
</tr>
</tbody>
</table>

VI. Special Considerations

A. Pure cultures of nonhemolytic Staph in numbers greater than 50,000 should have Staph saprophyticus ruled out. Refer to identification section.

B. Presence of diphtheroids, Lactobacillus species, small numbers of nonhemolytic Staph or Viridans Strep, or more than three different organisms indicate contamination of the specimen. The final report should be sent out with gross identification only, the floor should be notified and a repeat culture should be requested. The plates should be held on a bench with a three-day outdate.

C. Presence of a swarming Proteus species on sheep blood agar necessitates swooping from the SB to a phenylethyl alcohol agar plate streaking for isolation to rule out the presence of gram positive organisms. If present, the gram positive organisms should be identified and susceptibilities performed, if appropriate. It will not always be possible to quantitate the organisms. They will be reported out as being present.

VII. References


Sputum Culture

All work on sputums shall be performed under safety cabinet.

I. Screening

All sputum specimens submitted to the laboratory for routine culture shall be microscopically screened using Nomarski optics on a wet mount of the specimen. This shall be done as soon as possible after receipt and prior to plating the specimen onto culture media.

A. Procedure

1. Examine the sputum for the presence of blood and/or purulent material. A description of the specimen shall be recorded on the requisition prior to processing.

2. The most purulent, mucoid or blood-flecked portion shall be selected and transferred to a sterile petri dish. A portion of this material shall be transferred to a slide. Add a coverslip and gently press down without allowing the specimen to go beyond the coverslip edges.

3. Examine the direct wet mount under Nomarski optics at 100x magnification. Scan the entire slide to determine the distribution of cell types.

4. Select 10 representative fields and count the number of leukocytes (WBC) and squamous epithelial cells. Determine the average number of each cell type.

5. The following criteria shall be used to determine if the specimen shall be processed:

   Acceptable: less than 25 epithelial cells (EPC)
   Unacceptable: greater than 25 epithelial cells or less than 25 EPC if EPC > WBC.

6. Acceptable screen:

   a. Record the results of the Nomarski screen on the front of the laboratory requisition slip as follows:
Sputum screen -- acceptable: less than 25 epithelial cells

Note if no epithelial cells or no white blood cells are seen.

b. Process the sputum as indicated in Section II.

7. Unacceptable screen:

a. Notify the physician and request a new specimen.

b. If a new specimen cannot be obtained or the physician insists that this specimen be worked up, process as indicated below:

Record on the back of the slip the physician notified and his request for workup. The results of the screen shall be recorded on the front of the slip as follows:

Sputum screen -- unacceptable: greater than 25 EPC.
Dr. _______ requested workup.

c. The sputums that are rejected shall be charged for a gram stain. The laboratory slip shall be sent out as follows:

Specimen felt to be unacceptable for culture due to presence of greater than 25 squamous epithelial cells per 100x microscopic field.

Please repeat collection.
J. Matsen, M.D.

including the date and the initials of the technologist completing the work.

8. All sputums shall be saved in the bucket in the refrigerator for at least two days prior to discarding.
II. Culture (for all sputums except from cystic fibrosis patients)

A. Materials

1. Columbia blood agar plate (SB)
2. Horse blood agar plate (HB)
3. MacConkey agar plate (Mac)

B. Procedure

1. The remaining portion of purulent material in the petri dish shall be used to incubate the SB, HB, Mac. Streak each plate for isolation. Cuts should be made in the SB to enhance observation of oxygen labile hemolysins.

2. The sheep blood and horse blood agar plates shall be incubated at 35°C in 5% CO₂; the MacConkey shall be incubated aerobically at 35°C.

3. After overnight incubation, all plates shall be examined, and a quantitative list of all organisms present shall be recorded on the back of the slip. Use the quantitation standards posted in each work area.

4. Normal respiratory flora present in the culture should not be further identified and can be reported out on the preliminary and final reports as: 4+ normal flora.

5. The following possible pathogens must be identified if isolated in the quantities listed or if predominant (equal to or greater quantity of the amount of normal respiratory flora):

a. Beta Strep Group A — any quantity
b. Strep pneumoniae — any quantity
c. Haemophilus influenzae — 2+ or greater
d. Staph aureus — 3+ or greater
e. Candida albicans — 3+ or greater
   If germ tube negative yeast are present. Save organism for 2 weeks.

f. Gram negative rods (August 1986 procedure change: Gram negative rods must be in predominance of normal flora in order to be identified, reported or receive susceptibility testing.)

   (1) 1+ quantity — include in normal flora
(2) 2+ quantity

(a) Note on back of slip
(b) Save original plate 3 days
(c) Include the presence of negative rods as a separate notation in the prelim and final reports:

"2+ gram negative rod." (see attached note)

(d) Attach the following slip to the final report:

"Gram negative rods in quantities of 2+ or less are not routinely identified on sputum cultures. However, these organisms have been saved for 3 days in the event that you desire further workup on this specific patient."

(3) 3+ or greater

(a) Pure isolate -- work up.
(b) Mixed gram negative rods. The physician shall be consulted by either the lab director on call or the technologist in order to determine which, if any, organisms shall be worked up and have sensitivities.

6. Susceptibility testing shall be performed when requested on:

- Staph aureus
- Haemophilus influenzae (B lactamase screen)
- Gram negative rods

in the quantities and conditions stated above. Susceptibility testing will be limited to every third day on the same organisms, from same specimen on same patient. Refer the request to the previous culture!

"See culture #10943 for susceptibilities."
7. A preliminary report shall be issued after the initial reading of the culture.
8. The SB and HB shall be reincubated for an additional 24 hours prior to the final report being issued (even if no pathogens are being worked up).
9. If no additional colony types are observed after two days' incubation, and identification of predominant organisms has been completed, the final report should be sent out, with the date and initials of the technologist completing the culture. The box indicating "No Beta Streptococci" should be checked in the absence of beta streptococci.
10. If no growth occurs after two days' incubation, the final report should be sent out as follows: "No growth after 2 days," with the date and initials of the technologist completing the culture.

III. Culture of Cystic Fibrosis Patients

The previous procedure shall be followed with the following exceptions:

A. A phenylethyl alcohol plate (PEA) shall be included in the initial plating.
B. The following organisms shall be identified in any quantity:
   1. Staph aureus
   2. Haemophilus influenzae
   3. Pseudomonas aeruginosa -- hold Mac plate 48 hours prior to inoculating biochemicals if more than one colony type present.

All mucoid strains of Pseudomonas shall be noted on the back of the slip as well as in the preliminary and final reports. For example:

"4+ Pseudomonas aeruginosa (4 strains-mucoid and nonmucoid)"

C. Susceptibility, if requested, shall be performed as described previously.

IV. References


# APPENDIX H

## NCCLS SUGGESTED GROUPINGS*

*Permission to reproduce this table from M100-S2 (Performance Standards for Antimicrobial Susceptibility Testing; Second Informational Supplement) has been granted by the National Committee for Clinical Laboratory Standards, 771 E. Lancaster Avenue, Villanova, PA 19085.

## TABLE 1

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REFERENCES


