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Boston University
A NEW RESOURCE ON DRUG THERAPY

By: Darryl S. Rich, Pharm.D., Director of Pharmacy Services

The Pharmacy Update makes its premier this month as not just another newsletter but rather a timely resource on the rapidly expanding field of drug therapy and to serve as official medium for informing practitioners at University Hospital on the actions of the Pharmacy and Therapeutics Committee of the Medical Staff.

The Pharmacy Update will be distributed monthly to practitioners at University Hospital by the Department of Pharmacy and will have the following feature sections:

Editorial: A timely editorial will inform practitioners of important drug therapy issues that face all of us at University Hospital.

Current Information on Drugs: This featured article will present a recent update on drug therapy and discuss appropriate uses for new drugs added to the UH Formulary as well as existing drugs on the Formulary. Many times the article will present a review of all drugs for a given class. This article will be written by a member of the Pharmacy staff and reviewed by a member of the Medical Staff. Guidelines on Drug Use approved by the P&T Committee may also be presented.

Policy and Procedure: This section will serve to inform practitioners of new policies and procedures in the Department of Pharmacy as well as review existing ones that are often misunderstood and/or which many are misinformed of.

Brief Notes: This feature will highlight quick statements of interest related to drug therapy do not deserve a full article. This could include a new law, a short FDA statement or the recall of a drug product from the market.

Actions of the P & T Committee:
This section will review actions at the last month's Pharmacy and Therapeutics Committee of the Medical Staff. Additions to the Formulary will be indicated, as will recommendations for deletion and deletions from the Formulary. Practitioners will have 6 weeks to comment on the recommendations for deletion from the Formulary before they become final. All such actions (additions to or deletions from the Formulary) will not become officially until printed in the Pharmacy Update. Drugs that were denied addition to the Formulary will also be presented as will their reason for denial. Other P&T Committee decisions will be briefly presented.

Copies of the Pharmacy Update will be mailed by to all physicians and house staff at University Hospital and to all Nursing Units. Copies will be posted at various locations throughout University Hospital. Copies will also be kept in special red binders at each Nursing Station for future reference. Additional copies can be obtained from the Pharmacy (H-204). Your comments are always welcome. We hope to make the Pharmacy Update a valuable new resource to you.

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In recent years, many new antibiotic agents have been introduced for the clinical use in treating systemic infections. The majority of these agents have been third generation cephalosporins and synthetic penicillins which have been targeted to treat infections caused by Pseudomonas aeruginosa. Many of these new antibiotics are useful in treating infections resistant to other antibiotics. However, these remarkably active antibiotics have some shortcomings that include:

1. Rapid development of resistance, particularly if used extensively.
2. High cost.

To address these issues, in April 1986, the Pharmacy & Therapeutics Committee of the Medical Staff approved a revised list of parenteral antibiotics on the UH Formulary that will be available for use at University Hospital. This change in the UH Formulary was developed in cooperation with the Microbiology Laboratory, the Department of Pharmacy, and the Department of Medicine Section on Infectious Diseases. It was reviewed and approved by the Executive Committee of the Medical Staff in May 1986. The antibiotics were chosen based on the current microbiological sensitivity of organisms at University Hospital and the cost of these agents. This article summarizes the approved changes on the UH Formulary and the rationale behind the decisions.

The currently approved antibiotics are listed in Table 1 below. They are classified into three categories:

<table>
<thead>
<tr>
<th>Category I: (General Use)</th>
<th>Category II: (Monitored)</th>
<th>Category III: (Restricted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved for general use with no restrictions.</td>
<td>Cefotizoxime (Ceftizox)</td>
<td>Cefotaxime (Clavoran)</td>
</tr>
<tr>
<td>The Pharmacy will dispense the antibiotics after the prescribing physician has completed a utilization form (available at nursing stations and from the Pharmacy). The completed form must be submitted to the Pharmacy. The Infectious Diseases Service and P&amp;T Committee will review all completed forms.</td>
<td>Ceftriaxone (Rocephin)</td>
<td>Cefoxitin (Mefoxin)</td>
</tr>
<tr>
<td>The Pharmacy will only dispense the antibiotic after approval have been received from the Infectious Diseases Section.</td>
<td>Ticarcillin/Clavunate (Timentin)</td>
<td>Ceftazadime (approved 6/86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem/Cilastatin (Primaxin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piperacillin (Piperacil)</td>
</tr>
</tbody>
</table>

*These agents have been determined to be therapeutic equivalents. The agent in the pharmacy will be dispensed when the other agents are prescribed.

Cephalosporins

First Generation Cephalosporins

(Cefazolin, Cefonocid, Cephalothin,Cephapirin)

These agents share the same spectrum of antibacterial activity and are considered therapeutic equivalents (with the exception of cefonocid which has poor coverage against Staph. aureus). The Pharmacy will stock the least expensive agent from this group (except cefonocid) as determined by competitive bidding or other means. When any of these agents are prescribed, the agent currently stocked in the Pharmacy will be automatically dispensed. It is important to remember that cephalothin and cephapirin are dosed every 4-6 hours, whereas cefazolin (Ancef, Kefzol) is dosed every 8 hours or greater. The physician will be contacted to adjust the dosing interval appropriately if therapeutic substitution occurs.
In recent years, many new antibiotic agents have been introduced for the clinical use in treating systemic infections. The majority of these agents have been third generation cephalosporins and synthetic penicillins which have been targeted to treat infections caused by *Pseudomonas aeruginosa*. Many of these new antibiotics are useful in treating infections resistant to other antibiotics. However, these remarkably active antibiotics have some shortcomings that include:

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**Category I: (General Use)**
Approved for general use with no restrictions.

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The Pharmacy will dispense the antibiotics after the prescribing physician has completed a utilization form (available at nursing stations and from the Pharmacy). The completed form must be submitted to the Pharmacy. The Infectious Diseases Service and P&T Committee will review all completed forms.

**Category III: (Restricted)**
The Pharmacy will only dispense the antibiotic after approval has been received from the Infectious Diseases Section.

<table>
<thead>
<tr>
<th>Table 1: Parenteral Antibiotics on the UH Formulary (approved 5/86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Category I (General Use)</strong></td>
</tr>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td>Metronidazole</td>
</tr>
<tr>
<td>Ampicillin *Nafcillin/Oxacillin</td>
</tr>
<tr>
<td>*Cefazolin/Cephalothin/Cephapirin</td>
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<tr>
<td>Clindamycin</td>
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<tr>
<td>Penicillin G</td>
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<tr>
<td>Chloramphenicol</td>
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<tr>
<td>Tetracycline</td>
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<tr>
<td>Doxycycline</td>
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<tr>
<td>Ticarcillin</td>
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<tr>
<td>Erythromycin</td>
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<tr>
<td>Co-trimoxazole</td>
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<tr>
<td>Gentamicin</td>
</tr>
<tr>
<td>Vancomycin</td>
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<tr>
<td><strong>B. Category II (Monitored)</strong></td>
</tr>
<tr>
<td>Ceftizoxime (Ceftizox)</td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin)</td>
</tr>
<tr>
<td>Ticarcillin/Clavunate (Timentin)</td>
</tr>
<tr>
<td><strong>C. Category III (Restricted)</strong></td>
</tr>
<tr>
<td>Cefotaxime (Claforan)</td>
</tr>
<tr>
<td>Cefoxitin (Mefoxin)</td>
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**Cephalosporins**

**First Generation Cephalosporins**
(Cefazolin, Cefonocid, Cephalothin,Cephapirin)
These agents share the same spectrum of antibacterial activity and are considered therapeutic equivalents (with the exception of cefonocid which has poor coverage against *Staph. aureus*). The Pharmacy will stock the least expensive agent from this group (except cefonocid) as determined by competitive bidding or other means. When any of these agents are prescribed, the agent currently stocked in the Pharmacy will be automatically dispensed. It is important to remember that cephalothin and cephalapirin are dosed every 4-6 hours, whereas cefazolin (Ancef, Kezol) is dosed every 8 hours or greater. The physician will be contacted to adjust the dosing interval appropriately if therapeutic substitution occurs.
Second Generation Cephalosporins
(Cefamandole, Cefotoxin, Cefotetan, Cefuroxime)
These agents have added coverage against certain organisms over first generation cephalosporins but still have serious deficiencies in their antimicrobial spectra and are twice as expensive as first generation cephalosporins. The use of other agents in place of second generation cephalosporins is warranted in virtually all circumstances at University Hospital. Cefotixin has been restricted to Infectious Diseases Service approval because of the development of resistance to cefotixin by Bacteroides fragilis at University Hospital, thus eliminating the only advantage it has over first generation agents. Cefotaxime and cefuroxime have been advocated in the treatment of community-acquired pneumonia, especially due to Hemophilus influenzae. Erythromycin, with or without penicillin may be equally effective for most commonly community-acquired pneumonias. Therapy should be individualized with additional antibiotics if extended coverage is required. Gram negative bacillary pneumonias may require the use of third generation cephalosporin. Cefotetan is too new an agent to properly evaluate at this time.

Third Generation Cephalosporins
(Cefotaxime, Cefoperazone, Ceftazidime, Ceftriaxone, Moxalactam)
There has been an explosion of new agents available in this group. These agents have generated much confusion and have contributed to the high cost of antimicrobial therapy during the past several years (being several times more expensive than first or second generation agents). When these agents were evaluated for efficacy against Gram-negative bacilli isolated at University Hospital, only a few agents were shown to be clearly valuable and were included on the Formulary. Cefotaxime (Claforan), Ceftizoxime (Cefizox) and Ceftriaxone (Rocephin) have been shown to be equivalent in their antimicrobial activity. There are, however, significant differences in dosing. Cefotaxime has a half-life of 0.9 to 1.7 hours with a recommended dosing interval of 6-8 hours in most patients. Ceftriaxone has a half-life of 1.4 to 1.9 hours and a dosing interval of 8-12 hours. Ceftriaxone has an unusually long half-life of 10.7 hours with a recommended dosing interval of every 24 hours, making it particularly useful for ambulatory & home care use. Taking into consideration these differences in dosing intervals, ceftriaxone is currently the least expensive agent among the three and should be considered the third generation cephalosporin of choice when broad coverage is needed. Cefotaxime was retained on the Formulary as a restricted agent for use in gram-negative bacillary meningitis. The use of cefotaxime is recommended only in this situation and requires the approval of the Infectious Disease Service. Ceftriaxone has been retained on the Formulary for home care and IM use only. Once experience is gained with the other third generation cephalosporins, this recommendation may be revised. Ceftazidime has been added to the Formulary on a restricted basis. This agent is one of the most active against Pseudomonas aeruginosa, yet is by far one of the most expensive cephalosporins. It is also very active against a broad spectrum of multiply resistant enteric Gram-negative rods isolated at University Hospital. It has been restricted to approval of the Infectious Disease Section. Moxalactam offers no advantages over other available third generation agents and has been associated with significant hematological toxicity. Cefoperazone is less active against Escherichia coli and Klebsiella pneumoniae strains isolated from University Hospital patients than other third generation cephalosporins and has no cost advantage. Hence these last two drugs were deleted from the Formulary.

Imipenem-Cilastatin
Over the past several months, Gram-negative rods resistant to multiple antibiotics have been isolated at an increased rate by the Microbiology Laboratory. To address this problem, imipenem/cilastatin has been included on the Formulary, restricted to I.D. approval. It is important to note that resistance can develop to imipenem as to other broad spectrum antibiotics. In addition, imipenem (like cefotixin) has proven to be a potent inducer of beta-lactamase activity which results in the destruction of most, if not all, beta lactam antibiotics (the penicillins & cephalosporins). If this occurs, there may not be an alternative antibiotic to provide life-saving therapy. It is recommended that an Infectious Disease consultation be obtained if this potent antibiotic is needed. It should also be noted that this agent is currently the most expensive antimicrobial agent available.

Penicillins
(Penicillin G, Ampicillin, Nafcillin, Oxacillin, Methicillin)
Penicillin G and ampicillin have been retained on the Formulary as useful agents in the treatment of selected infections. Nafcillin, methicillin and oxacillin are therapeutically equivalent in treating penicillin-resistant staphylococcal infections. Methicillin is rarely used anymore because of its renal toxicity compared to the other agents. The least expensive agent between nafcillin and oxacillin will...
be stocked in the Pharmacy (currently nafcillin) and will be dispensed if either agent is prescribed. Neither of these agents is appropriate in treating methicillin-resistant staphylococcal infections for which vancomycin remains the only agent available at present. It should be noted that there is grave concern that the overuse of vancomycin will lead to resistance for which other agents will not work. In addition, vancomycin is one of the most costly antibiotics available. It is recommended that vancomycin use be limited to cases where resistance to nafcillin/oxacillin is documented or highly suspected. It should be further noted that the recommended dosing interval for vancomycin is every 12-24 hours, with significant prolongation in dosing interval or dose reduction needed in renal dysfunction (see nomogram in package insert for product).

**Extended Spectrum Penicillins**

(Azlocillin, Carbenicillin, Mezlocillin, Piperacillin, Ticarcillin)

All extended spectrum penicillins possess a broad spectrum of activity against enteric Gram-negative bacilli. The major difference among these agents is in eradicating Klebsiella sp. and *Pseudomonas aeruginosa* infections. Carbenicillin is infrequently used because of poor coverage against *Pseudomonas aeruginosa* and high sodium load. In our hospital, the activity of ticarcillin and mezlocillin are virtually identical and the enhanced Klebsiella coverage of mezlocillin is not apparent. In addition, ticarcillin is less expensive than the other agents in this class and so it has been chosen for inclusion on the Formulary. Piperacillin is the most active of these agents against *P. aeruginosa*, however, it is extremely expensive and if used indiscriminately, resistance usually develops. Therefore, ticarcillin is recommended as the antibiotic of choice in this class. If an organism is resistant to ticarcillin, a combination of ticarcillin/clavulanic acid (Timentin) may be active (clavulanic acid is a beta lactamase inhibitor). Most of the resistance of enteric Gram-negative rods is due to the production of beta lactamase. An exception is *Pseudomonas aeruginosa*, where Timentin may not be active. In this instance, the addition of an aminoglycoside is strongly recommended to prevent the emergence of resistance that often occurs when these penicillins are used as single agents. Piperacillin should only be used in cases of microbiologically-defined infections resistant to other penicillins or cephalosporins. Another potential use for piperacillin is in surgical prophylaxis when anaerobic coverage is needed. Only 1-2 doses are necessary to provide prophylactic coverage. Metronidazole is another agent that may be used to provide anaerobic coverage and is substantially less expensive than piperacillin. Piperacillin is restricted to Infectious Diseases Service approval.

**Aminoglycosides**

(Amikacin, Gentamicin, Neomycin, Streptomycin, Netilmicin, Tobramycin)

These agents although relatively toxic, remain the agents of choice in the treatment of serious Gram-negative infections. Because of its toxicity neomycin use is limited to oral administration and streptomycin's use is limited as well. Tobramycin was removed from the Formulary because it has only a small advantage in spectrum over gentamicin (which costs 1/10th that of tobramycin), while tobramycin offers no advantage to gentamicin in reducing toxicity. Not enough experience has been gained at University Hospital with netilmicin to properly evaluate it. Amikacin, a much more costly aminoglycoside, has been reserved for treating patients infected with documented gentamicin resistance and for empiric therapy in areas of the hospital where organisms with multiple antibiotic resistance are recovered.

**Other Antibiotics**

The other antibiotics on the Formulary include the low cost agents of metronidazole, co-trimoxazole, erythromycin, chloramphenicol, tetracycline and doxycycline. The other high cost antimicrobials include clindamycin and vancomycin. The use of these agents is recommended only in cases where other less costly agents cannot be used.

**Summary**

The revised Formulary contains antibiotics necessary to provide high quality drug therapy for treating bacterial infections at University Hospital. It is, however, a dynamic resource. Newer agents will be reevaluated on a continuous basis as will the current agents. The Pharmacy & Therapeutics Committee of the Medical Staff will notify practitioners of future changes in the Formulary through this Newsletter. Questions about the antibiotics on the Formulary or problems in managing infections should be directed to the Infectious Disease Service.

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**P & T Committee Actions**

**June 1986**

**Additions to the Formulary:**

- Ceftazidime (Tazacef, Tazidime, Fortaz)- Restricted to Infectious Diseases Service Approval
- Flecanide (Tonocard)- Restricted to Cardiology Service Approval
- Sufentanil (Sufenta)- Restricted to Anesthesiology Use Only
Review of Pharmacy & Therapeutics Committee Actions
July 1985-June 1986

A. Additions to the Formulary
- Leuprolide (restricted to Medical and Surgical Oncology)
- Betoptic
- Pindolol
- Amiodarone (restricted to Cardiology Service Approval)
- Enalapril
- Imipenem-cilastatin (restricted to Infectious Diseases Service Approval)
- Ticarcillin-clavulanic acid (requires completion of Special Utilization Form)
- Ceftriaxone (requires completion of Special Utilization Form)
- Ceftizoxime (requires completion of Special Utilization Form)
- Midazolam (restricted to Anesthesiology)
- Sufentanil (restricted to Anesthesiology)
- Ceftazidime (restricted to Infectious Disease Service Approval)
- Flecainide (restricted to Cardiology Service Approval)

B. Denied Addition to the Formulary
- Acebutolol
- Bupranax
- Pilocarpine HS Gel

C. Deletions from the Formulary
- Cefamandole
- Cefoperazone
- Mezlocillin
- Moxalactam
- Tobramycin

D. Change in Status on the Formulary
- Cefotaxime (restricted to Infectious Diseases Approval)
- Cefoxitin (restricted to Infectious Diseases Approval)
- Piperacillin (restricted to Infectious Diseases Approval)
- Trazadone (removed from restriction)

E. Therapeutic Equivalents
- Cefazolin/Cephapirin/Cephalothin
- Nafcillin/Oxacillin

F. Enteral Product Formulary Changes
Additions
- Propac
- Pulmocare
- Sustacal HC, Chocolate
- Stresstein

Deletions
- Isocal
- Sustacal Vanilla