Role of the Pharmacy & Therapeutics Committee in the Academic Medical Center

Center for Drug Safety and Effectiveness
March 25, 2013

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Division of Clinical Pharmacology
Hospital Pharmacologist
The Johns Hopkins Hospital
Disclosures:

1) Research study supported by Pfizer finished recently.

2) Participating in research studies supported by Metrics Pharmaceuticals and Sanofi-Aventis.

3) I like industry.
Outline

I. Published experience elsewhere

II. Pharmacy and Therapeutics Committee at Johns Hopkins

III. Philosophy

IV. Topics of Interest

V. Case Presentations

VI. Concluding Remarks
“Yeah, this is the pharmacy... Can’t you read the sign?”
“Pharmacy and Therapeutics (P&T) Committees have traditionally evaluated and developed policies for the clinical use of medications and for ensuring safe and effective drug use and administration.”

Mittleman N and Knowles S.
“...the initial focus of early hospital-based Pharmacy and Therapeutics committees was to outline a rational approach to medication use.”

Perrone J and Nelson LS

J Med Toxicol 2011
“Restricting the formulary helps clinicians by recommending particular medications on a hospital formulary, and streamlines pharmacy administration, controls expenses, and creates opportunities to limit errors by narrowing the spectrum of available medications.”

Perrone J and Nelson LS
J Med Toxicol 2011
“The potential to apply best-practices and evidence-based medicine, if done using an intellectually rigorous approach, should improve patient outcome and satisfaction while controlling cost and risk, the ultimate goals of the modern healthcare system.”

Perrone J and Nelson LS
J Med Toxicol 2011
EDITORIALS

Outcomes, Outcomes, Every where, nor any Stop to Think?

Colin P. West, MD, PhD\textsuperscript{1,2}

\textsuperscript{1}Division of General Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA; \textsuperscript{2}Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA.
“.....inconsistent or even inappropriate construction of composite endpoints is a common and completely avoidable threat to appropriate understanding and interpretation of trial results.”

West CP
J Gen Intern Med 2011; 26:1239-40
“At the very least, results for each component of a composite endpoint should be presented, and it does not seem too much to ask that composite endpoints be interpreted with thoughtful consideration of the relative importance of their components.”

West CP
J Gen Intern Med 2011; 26:1239-40
“Since approval by the FDA does not necessarily imply a therapeutic or safety advantage over existing therapy, an independent assessment of the safety and possible benefit of the drug (over existing drugs) must be performed.”

Perrone J and Nelson LS
J Med Toxicol 2011
Decisions by drug and therapeutics committees on the availability of medicines should be informed by evidence on cost-effectiveness as well as clinical effectiveness and safety.

Economic evaluations are quantitative methods by which health economists assess the cost-effectiveness of medicines and other healthcare interventions.

The usual measure of health outcome in economic evaluations is the quality-adjusted life-year (QALY) which allows comparisons to be made across the full range of clinical areas.

A medicine is generally considered to be cost-effective if each additional QALY gained by using it costs less than £20,000–30,000.

There are sometimes reasons for approving the use of a medicine (or its inclusion in a formulary) despite economic evidence that it is not cost-effective.
“….also charged with reviewing emerging safety data, FDA mandated boxed warnings, and postmarketing surveillance toxicity data to determine when a drug should no longer be used (formulary deletions) or used in limited settings in the hospital (restricted use).”

Perrone J and Nelson LS
J Med Toxicol 2011
“...the P&T Committee may be asked to investigate an adverse drug event or perform a root cause analysis following a medication error or serious adverse event. The goal of this process is to devise methods for improving the drug utilization processes in the hospital.”

Perrone J and Nelson LS
J Med Toxicol 2011
“A related challenge faced by P&T committees is the use of medications outside of their approved indications. This so called ‘off label’ prescribing is widely practiced and the data viewed by a P&T committee upon considering a new drug for formulary addition generally lacks off label use information. In pediatric pharmacotherapy this is particularly important given the persistent lack of appropriate age-based data for the vast majority of medications that are administered to children.”

Perrone J and Nelson LS
J Med Toxicol 2011
“Additionally, issues such as ‘use of own medications’ or ‘use of alternatives therapies’ are increasingly common during inpatient hospitalizations, and the committee must work to develop appropriate policies to prevent errors in this process while addressing the liability concerns of hospital administration and legal departments.”

Perrone J and Nelson LS
J Med Toxicol 2011
<table>
<thead>
<tr>
<th>Country</th>
<th>Authors</th>
<th>By hospital size</th>
<th>Number of meetings per year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Pedersen et al. [7]</td>
<td>Total</td>
<td>7.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50 beds</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–99 beds</td>
<td>6.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100–199 beds</td>
<td>7.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200–299 beds</td>
<td>7.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300–399 beds</td>
<td>9.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;400 beds</td>
<td>9.6</td>
</tr>
</tbody>
</table>
“Also, the attempt by the FDA to improve the safety of certain medications through the use of Risk Evaluation and Mitigation Strategies (REMS) has expanded the regulatory role for the P&T committee. Although many of these apply to individual prescribers and patients in unique situations, certain REMS require the participation of the medical center in validating credentials and practices.”

Perrone J and Nelson LS
J Med Toxicol 2011
“A recent development, now increasingly faced by P&T committees, is how to respond to drug shortages. As raw product and production processes are limiting some drug manufacturing, sudden drug shortages occur causing a rapid search for reasonable and safe interim alternatives.”

Perrone J and Nelson LS
J Med Toxicol 2011
The Shortage of Essential Chemotherapy Drugs in the United States

Mandy L. Gatesman, Pharm.D., and Thomas J. Smith, M.D.

For the first time in the United States, some essential chemotherapy drugs are in short supply. Most are generic drugs that have been used for years in childhood leukemia and curable cancers —
“The increasing number of ‘me too’ drugs (within a prescribing class) approved by the FDA adds to the difficulty in choosing the safest, most effective, and least costly drug while allowing for some physician autonomy in prescribing.”

Perrone J and Nelson LS
J Med Toxicol 2011
JHH Bylaws Duties and Responsibilities of the Pharmacy & Therapeutics Committee

1.) Serve in an evaluative, educational and advisory capacity to healthcare providers

Newsletter
2.) Develop a formulary of drugs accepted to use at The Johns Hopkins Hospital and provide for its revision as required. The formulary shall be reviewed at least annually. The selection and deletion of formulary items shall be based upon objective evaluation of their relative therapeutic merits, safety, and estimated cost impact.

Rational Therapeutics
Elements of Rational Therapeutics

1. Efficacy

2. Safety

3. Cost
“But it can’t hurt him”
Surrogate markers vs. “hard clinical endpoints”

Interleukin-2 Therapy in Patients with HIV Infection

NEJM 2009; 361:1548
<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Years 0</th>
<th>Years 1</th>
<th>Years 2</th>
<th>Years 3</th>
<th>Years 4</th>
<th>Years 5</th>
<th>Years 6</th>
<th>Years 7</th>
<th>Years 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>SILCAAT, interleukin-2 + ARV</td>
<td>849</td>
<td>722</td>
<td>650</td>
<td>635</td>
<td>648</td>
<td>623</td>
<td>597</td>
<td>447</td>
<td>254</td>
</tr>
<tr>
<td>SILCAAT, ARV alone</td>
<td>845</td>
<td>754</td>
<td>679</td>
<td>666</td>
<td>632</td>
<td>632</td>
<td>603</td>
<td>453</td>
<td>233</td>
</tr>
<tr>
<td>% Receiving interleukin-2 during yr</td>
<td>97.8</td>
<td>39.8</td>
<td>23.6</td>
<td>18.4</td>
<td>14.8</td>
<td>12.0</td>
<td>7.5</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>ESPRIT, interleukin-2 + ARV</td>
<td>2071</td>
<td>1890</td>
<td>1842</td>
<td>1809</td>
<td>1768</td>
<td>1732</td>
<td>1415</td>
<td>887</td>
<td>297</td>
</tr>
<tr>
<td>ESPRIT, ARV alone</td>
<td>2040</td>
<td>1928</td>
<td>1862</td>
<td>1803</td>
<td>1740</td>
<td>1649</td>
<td>1349</td>
<td>831</td>
<td>255</td>
</tr>
<tr>
<td>% Receiving interleukin-2 during yr</td>
<td>96.2</td>
<td>37.9</td>
<td>28.7</td>
<td>22.3</td>
<td>17.7</td>
<td>13.7</td>
<td>12.5</td>
<td>9.6</td>
<td></td>
</tr>
</tbody>
</table>
### A  Opportunistic Disease or Death from Any Cause (Primary End Point)

<table>
<thead>
<tr>
<th>Years</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>849, 810, 785, 764, 732, 702, 686, 499, 258</td>
</tr>
<tr>
<td>1</td>
<td>846, 814, 782, 748, 710, 685, 654, 496, 249</td>
</tr>
<tr>
<td>2</td>
<td>2071, 2030, 1998, 1948, 1910, 1874, 1552, 974, 322</td>
</tr>
<tr>
<td>3</td>
<td>2040, 2003, 1963, 1919, 1884, 1825, 1486, 909, 271</td>
</tr>
</tbody>
</table>

- **SILCAAT, interleukin-2 + ARV**
- **SILCAAT, ARV alone**
- **ESPRIT, interleukin-2 + ARV**
- **ESPRIT, ARV alone**
B  Death from Any Cause

<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SILCAAT</strong></td>
<td></td>
</tr>
<tr>
<td>interleukin-2 + ARV</td>
<td>849 825 803 787 759 733 720 529 275</td>
</tr>
<tr>
<td>ARV alone</td>
<td>846 829 804 784 756 730 709 542 277</td>
</tr>
<tr>
<td><strong>ESPRIT</strong></td>
<td></td>
</tr>
<tr>
<td>ARV alone</td>
<td>2040 2018 1989 1956 1923 1875 1533 940 291</td>
</tr>
</tbody>
</table>
Despite a substantial and sustained increase in the CD4+ cell count, as compared with antiretroviral therapy alone, interleukin-2 antiretroviral therapy yielded no clinical benefit in either study.

“...absolute risk reductions are not detailed in many clinical trials with positive results. This limitation of the literature continues despite the fact that reporting absolute risk measures is recommended by current guidelines endorsed by most prominent medical journals.”

West CP
J Gen Intern Med 2011; 26:1239-40
“There is truly an ocean of evidence surrounding us but if we imbibe indiscriminately it is our patients who suffer. ‘Enlightened skepticism’ (in keeping with the theme, taking published findings with a grain of salt) seems especially prudent if we are to successfully navigate these seas.”

West CP

J Gen Intern Med 2011; 26:1239-40
3.) Monitor and evaluate adverse drug reactions and medication errors; make appropriate recommendations for system changes to prevent such occurrences

MERIT
4.) Develop programs and procedures that help ensure ongoing cost-effective use of drugs with emphasis placed on clinical effectiveness, safety and total cost of therapy

Financial Implications Subcommittee
<table>
<thead>
<tr>
<th></th>
<th>Percent of GDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>15.7</td>
</tr>
<tr>
<td>France</td>
<td>11.0</td>
</tr>
<tr>
<td>Germany</td>
<td>10.4</td>
</tr>
<tr>
<td>Canada</td>
<td>10.1</td>
</tr>
<tr>
<td>Australia</td>
<td>8.9</td>
</tr>
<tr>
<td>UK</td>
<td>8.4</td>
</tr>
</tbody>
</table>

GDP = gross domestic product.

Table 1: Percent of GDP spent on health care in 2007
Figure 1: US total health-care spending by service in 2009 (US$ billion)
“Rationing is a reality in publicly funded health systems.”

“NICE has established a maximum threshold for drug coverage at £30,000 (around $50,000) per QALY gained, although a higher threshold is used for end-of-life drugs... based on a 1982 calculation. After adjustment for health-care inflation (around 5.5% annually over the last 30 years), this cutoff would now be equivalent to about $200,000 per QALY.”

“WHO has proposed using the wealth of an individual country when deciding on thresholds for economic value—specifically, multiples of a country’s per-capita GDP. New treatments with an ICER of less than or equal to the per-capita GDP would be considered very cost effective, one to three times the GDP would be cost effective and more than three times would be cost ineffective.”

Lancet Oncol 2011; 12:933-80
“...for high-income countries such as the USA, the cost per QALY threshold would be about $140,000.”

Drug charges ÷ Total hospital charges
= Drug charge fraction

Typically around 8%

With only one exception, <10%
Eculizumab

A monoclonal antibody that binds with high affinity to C5, which inhibits cleavage to C5a and C5b, thus preventing the generation of the terminal complement complex. This stops complement-mediated cell damage.

Black Box Warning: Meningococcal infections
Eculizumab for Antibody-Mediated Organ Transplant Rejection

20 patients for 23 inpatient admissions, 2007-2011
# Eculizumab Charges per Inpatient Admission

<table>
<thead>
<tr>
<th>Range</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>$8,743-579,249</td>
<td>$158,997</td>
<td>$120,750</td>
</tr>
</tbody>
</table>

# Eculizumab Charge Fraction per Inpatient Admission

<table>
<thead>
<tr>
<th>Range</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-70%</td>
<td>34.5%</td>
<td>35.8%</td>
</tr>
</tbody>
</table>
The Division of Drug Information (DDI) is CDER’s focal point for public inquiries. We serve the public by providing information on human drug products and drug product regulation by FDA.

The U.S. Food and Drug Administration today approved Soliris (eculizumab) to treat patients with atypical Hemolytic Uremic Syndrome (aHUS), a rare and chronic blood disease that can lead to kidney (renal) failure and is also associated with increased risk of death and stroke.

Atypical HUS accounts for 5 to 10 percent of all cases of hemolytic uremic syndrome. The disease disproportionately affects children.

Soliris is a targeted therapy that works by inhibiting proteins that play a role in aHUS. The FDA first approved Soliris in March 2007 to treat paroxysmal nocturnal hemoglobinuria (PNH), a rare type of blood disorder that can lead to disability and premature death. Soliris is classified as an orphan drug. Orphan drugs are those that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

There are no other FDA-approved treatments for aHUS, and the safety and effectiveness of current standard treatment, plasma therapy (plasma exchange or fresh frozen plasma infusion), have not been studied in well controlled trials.
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There are no other FDA-approved treatments for aHUS, and the safety and effectiveness of current standard treatment, plasma therapy (plasma exchange or fresh frozen plasma infusion), have not been studied in well controlled trials.
5.) Develop and monitor policies involving restrictions placed on the use of formulary and non-formulary drugs at The Johns Hopkins Hospital.

Open vs. Closed Formulary

Antimicrobial restrictions
Open formulary = unrestricted drug choices

Closed formulary = constrained drug choices
Antimicrobial formularies: Can they minimize antimicrobial resistance?

Maybe

Polk RE, Am J Health Syst Pharm 2003; 60 Suppl 1:516-19
The combination of a formulary restriction (rigors or procedural sedation only) along with a computerized order entry intervention and education of the changes to prescribers reduced parenteral meperidine analgesia from 20% to 0.1% at Strong Memorial Hospital in Rochester, N.Y.

6.) Review and approve all critical pathways, order sets, relevant research protocols and similar materials in which commercially available and investigational drugs are used. This may be accomplished by the Committee as a whole, or as delegated to a subcommittee or to individual members.

IRB Liaisons
7.) Develop and maintain policies and procedures involving the distribution and use of complimentary and alternative medications

CAM Policy
8.) Provide professional and scientific input to the service and education functions of the Department of Pharmacy.

Hospital Pharmacologist and other Committee members
9.) Educate physicians and other professional staff on matters pertaining to the use of drugs.

Ideal Therapeutic Algorithm
Ideal Therapeutic Algorithm

1. Determine the therapeutic goal.
2. Choose an appropriate agent.
3. Choose the appropriate dose, individualizing for each patient when possible.
4. Know when/how to monitor for effectiveness and safety, including the essential criteria for appropriate therapeutic drug monitoring.
5. Know how to adjust the therapy (e.g., increase the dose, add another medication, switch to another agent, etc.) to attain the therapeutic goal and avoid toxicity.
Criteria for Appropriate Therapeutic Drug Monitoring

1. Medication concentration or effects can be measured reliably and accurately

AND

2. The efficacy of medication treatment can be enhanced by achieving a certain concentration or effect range

AND/OR

3. The toxicity of medication treatment can be reduced by maintaining a certain concentration or effect range
Individualized Therapy

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Screening cut rate of hypersensitivity by over 50% (3.4% vs. 7.8%)

Mallal, S et al.
NEJM 2008; 358:568
Individualized Therapeutics

Drug level targets differ among individuals. Not all patients handle drugs alike. Patients & targets change over time.

Therefore, in clinical situations, you must:

• Analyze an individual’s regimen
• Design an individual’s regimen
• Modify an individual’s regimen
Measuring drug concentrations (or an appropriate physiological surrogate, such as aPTT) establishes individual pharmacokinetics.

One well-done drug concentration is more valuable than any algorithm, genetic information or prediction model
Warfarin

Do you load with warfarin?

Is it critical to know about 2D9 polymorphisms?

Not only genetics, but also diet, coexisting medical problems and concomitant medications affect warfarin dosing.
**Table 1 Pharmacoeology: environmental influences on drug disposition and response**

<table>
<thead>
<tr>
<th>Known environmental influences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food effects on drug absorption and bioavailability</td>
</tr>
<tr>
<td>Pharmacokinetic drug interactions</td>
</tr>
<tr>
<td>Pharmacodynamic drug interactions</td>
</tr>
<tr>
<td>Interactions with herbal medicines and nutritional supplements</td>
</tr>
<tr>
<td>Cultural, social, and economic influences on adherence</td>
</tr>
<tr>
<td>Individual drug-taking behavior&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intercurrent diseases, especially those affecting target organs for drug effect or drug elimination&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diurnal variation in pharmacokinetics and pharmacodynamics&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postulated/speculative environmental influences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental toxins, especially those affecting target organs for drug effect or drug elimination</td>
</tr>
<tr>
<td>Chemical contaminants of marketed drugs</td>
</tr>
<tr>
<td>Alterations in normal bacterial flora</td>
</tr>
<tr>
<td>Total food intake/body mass&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exercise routine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Factors likely to reflect combined environmental and genetic influences.
10.) Monitor and evaluate the use of Controlled Substances (as defined by the DEA) to assure that these substances are properly controlled and that all appropriate regulatory standards are maintained.

Controlled Substances Subcommittee
11.) Monitor and develop policies regarding the activities of pharmaceutical sales representative within the Hospital

Pharmaceutical Sales Representatives Policy
P&T Subcommittees and Chairs

Anesthesia/Analgesia Subcommittee
- chair, Tracey Stierer, M.D.

Antimicrobials Subcommittee
- chair, Pam Lipsett, M.D.

Chemotherapy Subcommittee
- chair, John Fetting, M.D.

Controlled Substances Subcommittee
- chair, Gary Flax, Pharm. D.
Drug Use Surveillance Team (DUST)
  -chair, Brian Pinto, Pharm. D.

Financial Implications Subcommittee
  -chair, Ed Beranek

Medication Event Reduction Improvement Team (MERIT)
  -chair, Bob Feroli, Pharm.D

Quick Response Subcommittee (QRS)
  -chair, Meg Garrett, Esq.
Institutional Review Board

P&T Liaisons

IRB 1- Hye Kim, Pharm. D.

IRB 2- Craig Hendrix, M.D.

IRB 3- Glenn Treisman. M.D., Ph.D.

JHSPH IRB- Vivian Rexroad, Pharm.D.

IRB 6- Andrew Stolbach, M.D.
Rigorous clinical trials that demonstrate effect of P&T Committees

Hard clinical endpoints

- patient survival (inpatient or after discharge or both)
- reduced toxicity
- reduced length of stay
Off-Label vs. Experimental Use
Off-Label Use and Medicare Reimbursement

Compendia

1.) American Hospital Formulary Service Drug Information
2.) National Comprehensive Cancer Network Drugs and Biologics Corpendium
3.) Thomson Micromedex DRUGDEX ®
4.) Clinical Pharmacology (online database), Gold Standard Inc.

These failing, need HINN or ABN form
“Therapeutic Inertia”

Stress ulcer prophylaxis:

Excessive- Am J Health-Syst Pharm 2007

Cost-ineffective in patients other than “high risk ICU patients- Arch Intern Med 2011

Discontinuation often successful- J Manag Care Pharm 2009
Medication Reconciliation
Rasburicase
Catalyzes oxidation of uric acid into allantoin, an inactive and soluble metabolite

Indication: Hyperuricemia due to malignancy in patients with or at risk for tumor lysis syndrome.

Dose: 0.17-0.2 mg/kg once daily for up to 5 days.

Cost: $600/1.5 mg vial
Rasburicase may cause severe hypersensitivity reactions, including anaphylaxis, hemolysis in patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency, and methemoglobinemia. Therapy should be immediately and permanently discontinued in any patient developing these conditions. Rasburicase will cause enzymatic degradation of the uric acid within blood samples left at room temperature, resulting in spuriously low uric acid levels.
Rasburicase

Patient with kidney disease, both nephrotic syndrome and acute renal failure, with elevated BUN, creatinine and uric acid (18/mg/dL). Because of nephrotoxicity of uric acid, wish to use rasburicase to decrease uric acid level.
Conclusion

1. There are many benefits to a strong Pharmacy and Therapeutics Committee
2. The Pharmacy and Therapeutics Committee at JHH is doing a good job
3. For the future, I believe that we should take on more seriously the financial implications of our decisions and consider value (e.g., QALY) in our decisions
4. Rigorous clinical evidence remains paramount
Acknowledgements

Technical Assistance
Latasha Simms

Collecting Relevant Literature
Bob Feroli
Todd Nesbit
Andrea Tanzella