TB and the Older Patient

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Definition of an “older” patient

- “Mature”
- “Elderly”
- Geriatric:
  - usually ≥ 65 years old
Our Aging Population

- 76 million individuals born in the “Baby Boom” between 1946-1964
- Immigration increased significantly with the passage of the Immigration Act of 1965
- Approximately 76.4 million “Baby Boomers” in the US today
- By 2029, individuals age 65 and older will make up 20% of the US population (vs. 14% in 2012)

Number of people age 65 and over, by age group, selected years 1900–2006 and projected 2010–2050

Note: Data for 2010–2050 are projections of the population.
Reference population: These data refer to the resident population.
Other contributions to growing older population:

- Preventive health measures
- Medications
- Other therapies/interventions that help treat chronic disease
- Average life expectancy: 78.49 years (2012)
Age is just a number…

By Fred Kashi. Aging In America
Or is it?

By Fred Kashi. Aging In America
TB in the United States

• Since 1993, case rates of TB have declined for all age groups by >50%
• The highest burden of disease continues to be among older adults
• 2012 case rate for all ages: 3.2/100,000
• 2012 case rates for age >65: 5.1/100,000

TB Case Rates* by Age Group
United States, 1993–2012

Cases per 100,000

Age Group (years)

Updated as of June 10, 2013.
“The geriatric population in developed countries, such as the United States, represents a large reservoir of tuberculosis infection across all ethnic and sex subsets.”
TB in the Older Patient

• The majority of TB in older patients is secondary to reactivation of LTBI.
• With age, the T-cell mediated immune response wanes allowing for latent TB to become active.

Kaufmann SHE. Nature Reviews Immunology 2001;1:20-30
Other factors contributing to reactivation of TB include:

- Age-associated diseases:
  - Malignancy, Diabetes
- Poor nutrition
- Chronic renal failure
- Chronic institutionalization:
  - 2-3 fold higher incidence of TB in nursing home residents

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Effects of aging</th>
<th>Prescribing implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition</td>
<td>Progressive reduction in total body water and lean body mass</td>
<td>Higher systolic arterial pressure</td>
</tr>
<tr>
<td></td>
<td>Increase in body fat</td>
<td>Increased impedance to left ventricular ejection</td>
</tr>
<tr>
<td>Cardiac and peripheral vascular</td>
<td>Heart changes (stiffening, reduced muscle strength)</td>
<td>Left ventricular hypertrophy and interstitial fibrosis</td>
</tr>
<tr>
<td>system</td>
<td>Reduction in the intrinsic heart rate</td>
<td>Reduced response to postural changes</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis and loss of elasticity of vessel walls</td>
<td>Increased heart rate</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Increased sensitivity</td>
<td>Enhanced response to CNS agents</td>
</tr>
<tr>
<td></td>
<td>Decreased blood flow</td>
<td>Slower mobility and voluntary motor activity</td>
</tr>
<tr>
<td></td>
<td>Decline in receptors and pathways (fewer brain cells and connections)</td>
<td>Delirium</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased secretion of hydrochloric acid and pepsin</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Dysfunction in GI motility</td>
<td>Reduced absorption and metabolism of several drugs</td>
</tr>
<tr>
<td></td>
<td>Decreased GI blood flow</td>
<td></td>
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<tr>
<td></td>
<td>Reduction in liver volume and blood flow</td>
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</tr>
<tr>
<td>Immune system</td>
<td>Decreased immunity to diseases</td>
<td>Increase in antibiotic use</td>
</tr>
<tr>
<td></td>
<td>Greater susceptibility to infections</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Loss of muscle tissue</td>
<td>Increased use of analgesic and anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
<td>Increased risk of falls and fractures</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Prolonged effects of drugs poorly excreted by the kidney</td>
</tr>
<tr>
<td>Renal</td>
<td>Reduction of renal mass and blood flow</td>
<td>Loss of strength and endurance of lungs with some drugs</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Vital capacity and FEV may decline with age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased rigidity of chest wall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced thorax muscle strength and endurance</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>Visual impairment, thickening and yellowing of the lens of the eye</td>
<td>Reduced adherence to drug therapies</td>
</tr>
<tr>
<td></td>
<td>Hearing impairment, loss of sensitivity for high-frequency tones and of discrimination of similar pitches</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decline in the ability to taste and smell</td>
<td></td>
</tr>
</tbody>
</table>

CNS, central nervous system; FEV, forced expiratory volume; GFR, glomerular filtration rate; GI, gastrointestinal.
By Fred Kashi. Aging In America
Case 1: A 94 yo with the “dwindles”

- 94 yo Filipino gentleman presents to local ER with the following: “generalized malaise, weakness, fatigue, decreased appetite, abdominal pain, and intermittent back pain”
- Abdominal pain started approximately two weeks earlier after a “fall”
- Denies fever, chills
- Son accompanies patient in ER, helps with translation
- Patient described as “cachectic” in appearance
- Past Medical History: Stroke, Diabetes, HTN
Diagnosed with:

- Acute renal failure due to dehydration
- Ileus
- Pneumonia
The Challenge of Diagnosing TB in an Older Adult

- *Lee et al.* found that in their study of young and elderly patients with pulmonary TB, initial diagnosis of TB was made correctly in 94.2% of younger patients, and only in 66.4% of elderly patients (p<0.0001)
- Pneumonia and lung cancer were the other diagnoses considered
- Less likely to have: hemoptysis, fever, night sweats
The Challenge of Diagnosing TB in an Older Adult

• Nonspecific symptoms are common including:
  - Chronic fatigue/weakness
  - Cognitive impairment
  - Anorexia/weight loss
  - Persistent low-grade fever
  - Changes in activities of daily living
• Symptom duration may be greater in the elderly
• May be confused with age-related illnesses:
  - malignancy
  - diabetes mellitus
  - malnutrition

Typical TB Chest X-ray

Hospital Course

- Treated for pneumonia
- Abdominal pain improved
- Discharged to follow-up with his primary care doctor
- Unfortunately, started to feel poorly again
- Findings on chest x-ray were unchanged
- Finally referred to see a pulmonologist
Making the Diagnosis

- Sputum collection may be more difficult because older people may have trouble coughing.
- Invasive procedure such as bronchoscopy may need to be performed to obtain sputum.
- Two-step TST recommended due to waning immune response.
Interferon Gamma Release Assays (IGRA)

- *Terbreugge et al.* analyzed 3263 Quantiferon Gold-in-Tube assays to determine impact of age on test performance
- Proportion of indeterminate results were significantly higher in pediatric (9.1%) and elderly (7.4%) than adult patients (2.6%)
- Majority of indeterminate tests due to failed positive controls

Making the Diagnosis

• Unable to produce sputum
• 5/10/13: underwent bronchscopy
• AFB smear negative
• 6/18/13: 1 of 3 specimens became AFB positive (grew one colony)
• 8/13: Started on TB therapy
Treatment

• Since most cases result from reactivation, drug resistance is less of a concern in elderly patients
• Resistance should be considered if patient is:
  1) From an area where there is a high prevalence of multi-drug resistance (MDR)
  2) A contact to a case with MDR
  3) Had previous inadequate treatment for active tuberculosis
### TABLE 3. ADJUSTED HAZARD OF ALL, OR SPECIFIC, SIDE EFFECTS IN ASSOCIATION WITH CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Any Serious*</th>
<th>Rash/Fever†</th>
<th>Hepatitis‡</th>
<th>GI Upset§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Female sex (versus male)</td>
<td>2.5</td>
<td>1.3 to 4.7</td>
<td>1.9</td>
<td>0.7 to 4.8</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–59 (versus &lt; 35)</td>
<td>1.7</td>
<td>0.8 to 3.8</td>
<td>1.0</td>
<td>0.3 to 3.1</td>
</tr>
<tr>
<td>60+ (versus &lt; 35)</td>
<td>2.9</td>
<td>1.3 to 6.3</td>
<td>1.3</td>
<td>0.4 to 4.1</td>
</tr>
<tr>
<td>From Asia (versus all others)</td>
<td>2.5</td>
<td>1.3 to 5.0</td>
<td>2.8</td>
<td>1.1 to 7.5</td>
</tr>
<tr>
<td>Method of detection passive (versus active)</td>
<td>2.5</td>
<td>0.9 to 6.6</td>
<td>2.3</td>
<td>0.6 to 8.3</td>
</tr>
<tr>
<td>Smear positive (versus smear negative)</td>
<td>1.3</td>
<td>0.7 to 2.6</td>
<td>1.0</td>
<td>0.4 to 2.7</td>
</tr>
<tr>
<td>Drug resistant (versus pansensitive)</td>
<td>1.8</td>
<td>0.8 to 4.3</td>
<td>1.0</td>
<td>0.2 to 4.5</td>
</tr>
<tr>
<td>Abnormal baseline LFTs (versus normal)</td>
<td>1.6</td>
<td>0.6 to 4.2</td>
<td>2.3</td>
<td>0.6 to 8.0</td>
</tr>
<tr>
<td>HIV-positive (versus negative or NA)</td>
<td>3.8</td>
<td>1.05 to 13.4</td>
<td>5.1</td>
<td>1.02 to 27</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** CI = confidence interval; Gl = gastrointestinal; HIV = human immunodeficiency virus; HR = hazard ratio; LFT = liver function test; NA = not available.

Boldface entries indicate statistically significant associations.

Hazard ratio and 95% confidence interval estimated from Cox multivariate proportional hazards modeling.

* Any serious side effects.
† Occurrence of rash or drug fever.
‡ Hepatitis defined as transaminases greater than three times the upper limit of normal with symptoms, or five times the upper limit of normal in the absence of symptoms.
§ Severe Gl intolerance: sufficient to cause discontinuation of some or all medications and/or hospitalization.
¶ Insufficient numbers, so estimates unstable.
¶¶ Before anti-TB therapy the liver transaminases were above the upper limit of normal.
Figure 3. Association of age with interval from start of therapy until occurrence of any major side effect (using Cox proportional hazards regression). *Solid line*, age 17 to 34 years; *dotted line*, age 35 to 59 years; *dashed line*, age 60 years and older. *Lines* truncated at time after which no further events occurred.
Hepatotoxicity

• Incidence of INH-associated hepatotoxicity increases with age:
  - risk of liver damage at age < 35: 0.3%
  - risk of liver damage at age > 50: 2.3%
  - severity of hepatitis also increases with age, with a higher mortality in patients older than 50
Treatment Course

• 8/4/2013 Started on RIPE
• Four weeks into therapy:
  - AST 400
  - ALT 580
• All medications held until LFTS normalized
• Isolate fully drug susceptible
• Restarted sequentially on: rifampin/ethambutol, INH
• Tolerated remainder of therapy
• Passed-away in mid-July due to “natural causes”
Outcomes

• Increased mortality due to TB noted in older populations
• *Wang et al.* reported:
  - 26.5% one-year mortality in patients >60
  - 4.1% one-year mortality in patients <60

HIV in Individuals >50 years old

- Individuals with HIV and a positive TST have a yearly risk for TB → 10%
- The number of people age ≥ 50 living with HIV/AIDS continues to increase
- In 2010, people age ≥ 50:
  - accounted for 5% of new HIV/AIDS diagnoses
  - accounted for 19% of people living with HIV infection in the US

http://www.cdc.gov/hiv/risk/age/olderamericans/
By Fred Kashi. Aging In America
Case: 83 yo with the “weak and dizzies”

- 83 yo African-American gentleman presents to local ER with complaints of: “extreme fatigue,” “severe weakness” in both legs for one week
- 30 lbs weight loss over previous 6 months
- Denies cough, shortness of breath, fever
- Admitted to hospital due to concern for malignancy or stroke
Case: Past Medical History

1. Diabetes mellitus
2. Hypertension
3. COPD
4. Peripheral vascular disease
5. Paroxysmal atrial fibrillation
6. History of colon surgery for an unknown cause with chronic diarrhea as a result
Case: Events during hospitalization

- Further discussion with patient and review of records revealed that he had been hospitalized at three different hospitals over the past 3-4 months for the same issues
- A CT scan of his Chest/Abdomen/Pelvis showed: multiple liver lesions, splenic masses, pleural effusion and significant lymphadenopathy
Case: Events during hospitalization

- A biopsy was performed due to concern for cancer
- Biopsy revealed: caseating granulomas
- A TST was placed—20 mm
- Patient was placed on 4 drug TB therapy and sent home
Case: Medications

1. Coumadin  
2. Actos  
3. Sotalol  
4. Omeprazole  
5. Celebrex  
6. Tylenol as needed  
7. Combivent  
8. Digoxin  
9. Welchol  
10. Lasix  
11. Zocor  
12. Hydralazine-reserpine-HCTZ  
13. Metoprolol  

Which of the above medications interact with Rifampin and may require additional monitoring or dose adjustment?
Drug Interactions

• Many elderly patients have multiple medical problems including:
  - Diabetes
  - Heart disease
  - Chronic lung disease
  - End-stage renal disease

• High potential for interaction between rifampin and other medications
# Drug Interactions

## Table 1. Rifampin Drug Interactions of Major Clinical Significance*

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulants</td>
<td>Monitor international normalized ratio; increased anticoagulant dose will likely be needed</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Use alternative form(s) of birth control; counsel patient and document in medical record</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Monitor serum cyclosporine concentrations; increased dosage will likely be needed</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Monitor arrhythmia control, signs and symptoms of heart failure, and serum digitoxin concentrations</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Increase dose of glucocorticoid 2- to 3-fold</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Prefer to avoid use with rifampin; if must use, increase dose and monitor response</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Avoid concomitant use if possible; if must use, increase dose and monitor response; space ketoconazole and rifampin doses by 12 h</td>
</tr>
<tr>
<td>Methadone hydrochloride</td>
<td>Increase methadone dose with concomitant rifampin therapy; monitor and control withdrawal symptoms</td>
</tr>
<tr>
<td>Midazolam or triazolam</td>
<td>Prefer to avoid use with rifampin; use another agent if possible</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Monitor serum phenytoin concentrations and seizure activity; increase dosage if needed</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Monitor serum quinidine concentrations and arrhythmia control; increase dosage if needed</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Monitor serum theophylline concentrations; increase dosage if needed</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Use an alternative agent to verapamil because large oral verapamil doses may not be adequate; monitor patient for clinical response†</td>
</tr>
</tbody>
</table>

*Data adapted from Bacieciwicz and coworkers,12 Borcherding et al,3 and Strayhorn et al.4 Carefully adjust doses when rifampin use is discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer.†See also data on diltiazem and nifedipine in Table 2.
Drug Interactions

Table 4. Updated Rifampin Drug Interactions*

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Controlled Drug Interaction Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin receptor (5-HT₃) antagonist⁴⁴,⁴⁶</td>
<td>Monitor clinical response; increase dose if needed; use another agent if needed</td>
<td></td>
</tr>
<tr>
<td>Buspirone hydrochloride¹¹,¹²</td>
<td>Monitor clinical response; increased dose will likely be needed or use another agent if possible</td>
<td></td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors¹⁷,¹⁸</td>
<td>Monitor lipid panel; increased dose will likely be needed for simvastatin; further research needed for other agents in this class</td>
<td></td>
</tr>
<tr>
<td>Metronidazole⁹⁵</td>
<td>Monitor for decreased clinical response; increase dose if needed or use another agent if possible</td>
<td></td>
</tr>
<tr>
<td>Opiates (morphine or codeine)⁴⁶-⁴⁸</td>
<td>Monitor pain control and clinical response; increased dose may be needed in extensive metabolizers; use another agent if possible; may be associated with ethnic variability</td>
<td></td>
</tr>
<tr>
<td>Propafenone hydrochloride²⁰,²¹</td>
<td>Monitor clinical response; increased dose may be needed or use another agent if possible</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen citrate or toremifene citrate⁹⁹</td>
<td>Monitor clinical response; increased dose likely needed</td>
<td></td>
</tr>
<tr>
<td>Zolpidem tartrate¹⁴</td>
<td>Monitor clinical response; increased dose may be needed or use another agent if possible</td>
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Potential Interactions Based on Case Reports†

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine⁹⁵</td>
<td>Monitor clinical response; increase dose if needed or use another agent if possible</td>
</tr>
<tr>
<td>Levothyroxine sodium⁶¹</td>
<td>Monitor thyrotropin level; increased dose likely needed</td>
</tr>
<tr>
<td>Sertraline hydrochloride⁹</td>
<td>Monitor clinical response; increase dose if needed</td>
</tr>
</tbody>
</table>

*Carefully adjust dosage when rifampin use is initiated and discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer when rifampin therapy is discontinued. Based on the small number of reports, further studies are needed for most of these agents.

†Controlled study is needed to establish the importance and extent of the interaction.

http://www.drugs.com/drug_interactions.html

Case: Issues at home

- Main complaint: nausea with medications
- Anti-nausea medications ineffective
- Encouraged to eat prior to meds→not helpful
- He was becoming increasingly difficult to DOT
Case: Home visit

• Lived with his elderly wife who was his main caregiver
• Concern about her level of literacy
• Patient and wife were very concerned about their friends knowing that the patient had TB
• A home health nurse helped the patient with his regular medications by filling pill boxes for him:
Case: Home Visit

- Carefully reviewed all TB medications with patient to see which ones in particular made him feel ill:

- Discussed whether he was actually receiving nausea medication and if it helped when he did get it

- Discussed eating schedule, the foods that he enjoyed, encouraged him to try these foods prior to taking the medications
Case: Plan--Part 1

• Discussion with patient’s primary care doctor’s office:
  - limit other unnecessary medications
  - change medications if possible to cut down on pill burden and less frequent dosing

• Communication with patient’s cardiologist as it seemed that some of the patient’s issues were related to his atrial fibrillation and not to TB issues
Case: Plan--Part 2

- Scheduled anti-nausea medications to be taken at the same time as DOT
- TB nurse would extend her visits with patient to talk to him and sit with him before and after taking medications to help build rapport, offer support and encouragement
Case: Outcome

- Scheduled anti-nausea medications helped
- Decreasing the amount of other medications the patient was taking was helpful
- TB nurse established terrific rapport with patient and his wife and he started to look forward to her visits
- Patient had a pacemaker placed which helped with his other symptoms and also decreased amount of medications he was taking
- He completed 9 months of therapy successfully
Lessons Learned

• Communication is key:
  - patient
  - caregiver
  - other providers
• Consider the whole patient
• Treating TB requires a team effort
• Be willing to be flexible
• Patience *is* a virtue
Appendix A: Additional Rifampin Drug Reactions

### Table 2. Rifampin Drug Interactions*

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Adrenergic blocking agents</td>
<td>Monitor patient for clinical response; increased propranolol hydrochloride or metoprolol dose may be needed</td>
</tr>
<tr>
<td>Chloramphenicol†</td>
<td>Monitor serum chloramphenicol concentrations; may need to increase dosage</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Monitor signs and symptoms of infection; more study needed</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Monitor clinical response; dosage increase may be necessary; additional study needed when used for <em>Pneumocystis carinii</em> prophylaxis; monitor for hematologic toxic effects</td>
</tr>
<tr>
<td>Diazepam†</td>
<td>Monitor clinical response; may need to increase diazepam dosage</td>
</tr>
<tr>
<td>Digoxin (oral)</td>
<td>Monitor arrhythmia control and signs and symptoms of heart failure; monitor digoxin serum concentrations</td>
</tr>
<tr>
<td>Diltiazem†</td>
<td>Use alternative agent if possible because large oral doses of diltiazem may be ineffective; monitor clinical response‡</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Monitor arrhythmia control; increase dosage if needed</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Monitor clinical response; increase dosage if needed</td>
</tr>
<tr>
<td>Fluconazole†</td>
<td>Monitor clinical response; may need to increase fluconazole dosage; less reduction in serum concentrations vs other azoles</td>
</tr>
<tr>
<td>Haloperidol†</td>
<td>Monitor clinical response; increase dosage if needed</td>
</tr>
<tr>
<td>Losartan potassium</td>
<td>Monitor patient for clinical response; may need to increase dosage</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Alternative class of agents should be considered; monitor clinical response; dosage increase may be needed†</td>
</tr>
<tr>
<td>Nortriptyline hydrochloride</td>
<td>Monitor clinical response and serum nortriptyline concentrations</td>
</tr>
<tr>
<td>Pefloxacin</td>
<td>Moderate rifampin induction effect; pending further research, no dosage adjustment recommended</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Monitor blood glucose levels; base any dosage adjustments on blood glucose control</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Monitor serum tacrolimus concentrations and clinical response; increased dose may be needed or use another agent if possible</td>
</tr>
<tr>
<td>Tocainide</td>
<td>Monitor arrhythmia control; increase dosage if needed</td>
</tr>
</tbody>
</table>

*Data adapted from Baciewicz and coworkers,1,2 Borcherding et al,3 and Strayhorn et al.4 Additional study is needed to clearly establish clinical significance. Carefully adjust doses when rifampin use is discontinued. The enzyme induction effect is gradually reduced during a 1- to 2-week period or longer.

†Probably of clinical significance.
‡See also data on verapamil in Table 1.