Infectious Diseases Specialist

• ....and what is it exactly that you do?
The fantastic world of Microbiology
Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8e

by John E. Bennett MD (Author), Raphael Dolin MD (Author), Martin J. Blaser MD (Author)

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Table of Contents

Part I Basic Principles in the Diagnosis and Management of Infectious Diseases

Section A. Microbial Pathogenesis

1 A Molecular Perspective of Microbial Pathogenicity
2 Microbial Adherence
3 Toxins

Section B. Host Defense Mechanisms

4 Innate (General or Nonspecific) Host Defense Mechanisms
5 Human Genetics and Infection
6 Antibodies
7 Complement
8 Granulocytic Phagocytes
9 Cell-Mediated Defense Against Infection
10 Nutrition, Immunity, and Infection
11 Probiotics
12 Evaluation of the Patient with Suspected Immunodeficiency

Section C. Epidemiology of Infectious Diseases

13 Epidemiologic Principles
14 Outbreak Investigation
15 Emerging and Reemerging Infectious Disease Threats
16 Hospital Preparedness for Emerging and Highly Contagious Infectious Diseases

Section D. Clinical Microbiology

17 The Clinician and the Microbiology Laboratory
Section E. Anti-Infective Therapy

18 Principles of Anti-infective Therapy
19 Molecular Mechanisms of Antibiotic Resistance in Bacteria
20 Pharmacokinetics and Pharmacodynamics of Anti-infective Agents
21 Penicillins
22 Ceplasporins
23 Other à-Lactam Antibiotics
24 à-Lactam Allergy
25 Fusidic Acid
26 Aminoglycosides
27 Tetracyclines and Chloramphenicol
28 Rifamycins
29 Metronidazole
30 Macrolides, Clindamycin, and Ketolides
31 Glycopeptides, Streptogramins, and Lipopeptides
32 Polymyxins (Polymyxin B and Colistin)
33 Oxazolidinones
34 Sulfonamides and Trimethoprim
35 Quinolones
36 Unique Antibacterial Agents
37 Urinary Tract Agents: Nitrofurantoin and Methenamine
38 Topical Antibacterials
39 Antimycobacterial Agents
40 Antifungal Agents
41 Antiviral Drugs (Other Than Antiretrovirals)
42 Immunomodulators
43 Hyperbaric Oxygen
44 Agents Active against Parasites and Pneumocystis
45 Complementary and Alternative Medicines for Infectious Diseases
46 Antimicrobial Management: Cost and Resistance
47 Interpretation of Clinical Trials of Antimicrobial Agents
48 Outpatient Parenteral Antimicrobial Therapy
49 Tables of Antimicrobial Agent Pharmacology
Part II Major Clinical Syndromes

Section A. Fever

50 Temperature Regulation and the Pathogenesis of Fever
51 Fever of Unknown Origin
52 The Acutely Ill Patient with Fever and Rash

Section B. Upper Respiratory Tract Infections

53 The Common Cold
54 Pharyngitis
55 Acute Laryngitis
56 Acute Laryngotracheobronchitis (Croup)
57 Otitis Externa, Otitis Media, and Mastoiditis
58 Sinusitis
59 Epiglottitis
60 Infections of the Oral Cavity, Neck, and Head

Section C. Pleuropulmonary and Bronchial Infections

61 Acute Bronchitis
62 COPD, Chronic Bronchitis, and Acute Exacerbations
63 Bronchiolitis
64 Acute Pneumonia
65 Empyema and Pleural Effusion
66 Lung Abscess
67 Chronic Pneumonia
68 Cystic Fibrosis

Section D. Urinary Tract Infections

69 Urinary Tract Infections

Section E. Sepsis

70 Sepsis, Severe Sepsis, and Septic Shock

Section F. Intra-abdominal Infection

71 Peritonitis and Intraperitoneal Abscesses
72 Infections of the Liver and Biliary System
73 Pancreatic Infections
74 Splenic Abscess
75 Appendicitis
76 Diverticulitis and Typhilitis
Section G. Cardiovascular Infections
77 Endocarditis and Intravascular Infections
78 Prosthetic Valve Endocarditis
79 Infections of Non-Valvular Cardiovascular Devices
80 Prophylaxis of Infective Endocarditis
81 Myocarditis and Pericarditis
82 Mediastinitis

Section H. Central Nervous System Infections
83 Approach to the Patient with Central Nervous System Infection
84 Acute Meningitis
85 Infections of CSF Shunts
86 Chronic Meningitis
87 Encephalitis, Myelitis, and Neuritis
88 Brain Abscess
89 Subdural Empyema, Epidural Abscess, and Intracranial Suppurative Thrombophlebitis

Section I. Skin and Soft Tissue Infections
90 Cellulitis, Necrotizing Fasciitis and Subcutaneous Tissue Infections
91 Myositis
92 Lymphadenitis and Lymphangitis

Section J. Gastrointestinal Infections and Food Poisoning
93 Principles and Syndromes of Enteric Infection
94 Esophagitis
95 Nausea, Vomiting, and Noninflammatory Diarrhea
96 Antibiotic-Associated Colitis
97 Inflammatory Enteritides
98 Enteric Fever and Other Causes of Abdominal Symptoms with Fever
99 Foodborne Disease
100 Tropical Sprue/Enteropathy
101 Whipple's Disease

Section K. Bone and Joint Infections
102 Infectious Arthritis
103 Osteomyelitis
104 Infections in Prostheses in Bones and Joints
Section L. Diseases of the Reproductive Organs and Sexually Transmitted Diseases

105 Genital Skin and Mucous Membrane Lesions
106 Urethritis
107 Vulvovaginitis and Cervicitis
108 Infections of the Female Pelvis
109 Prostatitis, Epididymitis, and Orchitis

Section M. Eye Infections

110 Microbial Conjunctivitis
111 Microbial Keratitis
112 Endophthalmitis
113 Infectious Causes of Uveitis
114 Periocular Infections

Section N. Hepatitis

115 Acute Hepatitis
116 Chronic Viral Hepatitis

Section O. Acquired Immunodeficiency Syndrome

117 Global Perspectives on HIV Infection and Acquired Immunodeficiency Syndrome
118 Epidemiology and Prevention of AIDS and HIV Infection
119 Diagnosis of Human Immunodeficiency Virus Infection
120 The Immunology of Human Immunodeficiency Virus Infection
121 General Clinical Manifestations of Human Immunodeficiency Virus Infection
122 Pulmonary Manifestations of Human Immunodeficiency Virus Infection
123 GI and Hepatobiliary Manifestations of Human Immunodeficiency Virus Infection
124 Neurologic Diseases Caused by HIV-1 and Opportunistic Infections
125 Malignancies in Human Immunodeficiency Virus Infection
126 Human Immunodeficiency Virus Infection in Women
127 Pediatric Human Immunodeficiency Virus Infection
128 Antiretroviral Therapy for Human Immunodeficiency Virus Infection
129 Management of Opportunistic Infections Associated with HIV Infection
130 Vaccines for Human Immunodeficiency Virus-1 Infection

Section P. Miscellaneous Syndromes

131 Chronic Fatigue Syndrome
Part III Infectious Diseases and Their Etiologic Agents

Section A. Viral Diseases

132 Introduction to Viruses and Viral Diseases - DNA Viruses - Poxviridae
133 Orthopoxviruses: Vaccinia, Variola, Monkeypox, and Cowpox
134 Other Poxviruses: Parapoxviruses, Molluscum Contagiosum, and Tanapox Herpesviridae
135 Introduction to Herpesviridae
136 Herpes Simplex Virus
137 Varicella-Zoster Virus
138 Cytomegalovirus
139 Epstein-Barr Virus (Infectious Mononucleosis)
140 Human Herpesvirus Types 6 and 7
141 Kaposi's Sarcoma-Associated Herpesvirus (Human Herpesvirus Type 8)
142 Herpes B Virus - Adenoviridae
143 Adenovirus - Papovaviridae
144 Papillomaviruses
145 JC, BK, and Other Polyomaviruses; Progressive Multifocal Leuкоencephalopathy - Hepadnaviridae
146 Hepatitis B Virus and Hepatitis Delta Virus - Paroviridae
147 Human Paroviruses - RNA Viruses - Reoviridae
148 Orthoreoviruses and Orbiviruses
149 Coltiviruses and Seadornaviruses (Colorado Tick Fever)
150 Rotaviruses - Togaviridae
151 Alphaviruses
152 Rubella Virus (German Measles) - Flaviviruses
153 Flaviviruses (Yellow Fever, Dengue, Dengue Hemorrhagic Fever, Japanese Encephalitis, West
154 Hepatitis C - Coronaviridae
155 Coronaviruses, Including SARS-Associated Coronavirus
Paramyxoviridae
156 Parainfluenza Viruses
157 Mumps Virus
158 Respiratory Syncytial Virus
159 Human Metapneumovirus
160 Measles Virus (Rubeola)
161 Zoonotic Paramyxoviruses: Hendra, Nipah, and Menangle Viruses
Rhabdoviridae
162 Vesicular Stomatitus Virus and Related Viruses
163 Rhabdoviruses - Filoviridae
164 Marburg and Ebola Virus Hemorrhagic Fevers - Orthomyxoviridae
165 Influenza Viruses Including Avian Influenza - Bunyaviridae
166 California Encephalitis, Hantavirus Pulmonary Syndrome, and Bunyavirid Hemorrhagic Fevers
167 Lymphocytic Choriomeningitis Virus, Lassa Virus, and the South American Hemorrhagic Fever:
168 Human T-Cell Lymphotropic Virus Types I and II
169 Human Immunodeficiency Viruses - Picornaviridae
170 Introduction to the Enteroviruses
171 Poliovirus
172 Coxsackieviruses, Echoviruses, and Newer Enteroviruses
173 Hepatitis A Virus - Caliciviridae and Other Gastrointestinal Viruses
174 Rhinovirus
175 Noroviruses and Other Caliciviruses
176 Astroviruses and Picobirnaviruses - Undclassified Viruses
177 Hepatitis E Virus
Section B. Prion Diseases

178 Prions and Prion Diseases of the Central Nervous System (Transmissible Neural Disease)

Section C. Chlamydial Diseases

179 Introduction to Chlamydial Diseases
180 Chlamydia trachomatis (Trachoma, Perinatal Infections, Lymphogranuloma)
181 Chlamydophila (Chlamydia) psittaci (Psittacosis)
182 Chlamydophila (Chlamydia) pneumoniae
183 Introduction to Mycoplasma Diseases
184 Mycoplasma pneumoniae and Atypical Pneumonia

Section D. Mycoplasma Diseases

185 Genital Mycoplasmas: Mycoplasma genitalium, Mycoplasma hominis, and Urogenital Mycoplasma

Section E. Rickettsioses, Ehrlichioses, and Anaplasmosis

186 Introduction to Rickettsioses, Ehrlichioses and Anaplasmosis
187 Rickettsia rickettsii and Other Spotted Fever Group Rickettsiae (Rocky Mountain spotted fever)
188 Rickettsia akari (Rickettsialpox)
189 Coxiella burnetii (Q Fever)
190 Rickettsia prowazekii (Epidemic or Louse-Borne Typhus)
191 Rickettsia typhi (Murine Typhus)
192 Orientia Tsutsugamushi
193 Ehrlichia Chaffeensis and Ehrlichia Phagocytophila
Section F. Bacterial Diseases

194 Introduction to Bacteria and Bacterial Diseases - Gram-Positive Cocci
195 Staphylococcus aureus (Including Staphylococcal Toxic Shock)
196 Staphylococcus epidermidis and Other Coagulase-Negative Staphylococci
197 Classification of Streptococci
198 Streptococcus pyogenes
199 Nonsuppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis
200 Streptococcus pneumoniae
201 Enterococcus Species: Streptococcus bovis, and Leuconostoc Species
202 Streptococcus agalactiae (Group B Streptococcus)
203 Viridans Streptococci. Groups C and G Streptococci, and Gemella morbillorum
204 Streptococcus anginosus Group - Gram-Positive Bacilli
205 Corynebacterium diphteriae
206 Corynebacteria other than Diphtheria and Rhodococcus
207 Listeria monocytogenes
208 Bacillus anthracis (Anthrax)
209 Bacillus Species and Other than Bacillus anthracis
210 Erysipelothrix rhusiopathiae - Gram-Negative Cocci
211 Neisseria meningitidis
212 Neisseria gonorrhoeae
213 Moraxella catarrhalis and Other Gram-Negative Cocci - Gram-Negative Bacilli
214 Vibrio cholerae
215 Other Pathogenic Vibrios
216 Campylobacter jejuni and Related Species
217 Helicobacter pylori and Other Gastric Helicobacter Species
218 Enterobacteriaceae
219 Pseudomonas species, including Ps. aeruginosa
220 Sterotrophomonas maltophilia and Burkholderia cepacia complex
221 Burkholderia pseudomallei and Burkholderia mallei
222 Acinetobacter Species
223 Salmonella Species, Including Salmonella typhi
224 Shigella Species (Bacillary Dysentery)
225 Haemophilus species (including H. influenzae and chancroid)
226 Brucella Species
227 Francisella tularensis (Tularemia)
228 Pasteurella Species
229 Yersinia Species, Including Plague
230 Bordetella Pertussis
231 Rat-Bite Fever Streptobacillus moniliformis and Spirillum minus
232 Legionella
233 Other Legionella Species
234 Capnocytophaga
235 Bartonella, Including Cat-Scratch Disease
236 Calymmatobacterium granulomatis (Donovanosis, Granuloma inguinale)
237 Other Gram-Negative and Gram-Variable Bacilli - Spirochetes
238 Treponema pallidum (Syphilis)
239 Endemic Treponematoses
240 Leptospirosis (Leptospirosis)
241 Borrelia Species (Relapsing Fever)
242 Borrelia burgdorferi (Lyme Disease, Lyme Borreliosis) - Anaerobic Bacteria
243 Anaerobic Infections: General Concepts
244 Clostridium tetani (Tetanus)
245 Clostridium botulinum (Botulism)
246 Gas Gangrene and Other Clostridium-Associated Diseases
247 Bacteroides, Prevotella, Porphyromonas, and Fusobacterium Species
248 Anaerobic Cocci Anaerobic
249 Anaerobic Gram-Positive Non-sporulating Bacilli - Mycobacterial Diseases
250 Mycobacterium tuberculosis
251 Mycobacterium leprae
252 Mycobacterium Avium-intracellulare
253 Infections due to Mycobacteria other than M. tuberculosis and M. Avium Complex - Higher Bacterial Diseases
254 Nocardia Species
255 Agents of Actinomycosis
Section G. Mycoses

256 Introduction to Mycoses
257 Candida Species
258 Aspergillus Species
259 Agents of Mucormycosis
260 Sporothrix schenckii
261 Agents of Chromomycosis
262 Agents of Mycetoma
263 Cryptococcus neoformans
264 Histoplasma capsulatum
265 Blastomyces dermatitidis
266 Coccidioides Species
267 Dermatophytosis and Other Superficial Mycoses
268 Paracoccidioides brasiliensis
269 Uncommon Fungi and Prototheca
270 Pneumocystis
271 Microsporidiosis

Section H. Protozoal Diseases

272 Introduction to Protozoal Diseases
273 Entamoeba species including amoebiasis
274 Free-Living Amebas
275 Plasmodium Species (Malaria)
276 Leishmania Species: Visceral, Cutaneous, and Mucocutaneous Leishmaniasis
277 Biology of Trypanosoma Species
278 Agents of African Trypanosomiasis (Sleeping Sickness)
279 Toxoplasma gondii
280 Giardia lamblia
281 Trichomonas vaginalis
282 Babesia Species
283 Cryptosporidium Species
284 Isospora belli, Sarcocystis Species, Blastocystis hominis and Cyclospora
Section I. Diseases Due to Toxic Algae

285 Human Illness Associated with Harmful Algal Blooms

Section J. Diseases Due to Helminths

286 Introduction to Helminth Infections
287 Intestinal Nematodes (Roundworms)
288 Tissue Nematodes, Including Trichinosis, Dracunculiasis, and the Filariases
289 Trematodes (Schistosomes and Other Flukes)
290 Cestodes (Tapeworms)
291 Visceral Larva Migrans and Other Unusual Helminth Infections

Section K. Ectoparasitic Diseases

292 Introduction to Ectoparasitic Diseases
293 Lice (Pediculosis)
294 Scabies
295 Myiasis and Tungiasis
296 Mites (Including Chiggers)
297Ticks (Including Tick Paralysis)

Section L. Diseases of Unknown Etiology

298 Kawasaki Syndrome
Part IV Special Problems

Section A. Nosocomial Infections

299 Organization for Infection Control
300 Isolation
301 Disinfection, Sterilization, and Control of Hospital Waste
302 Infections Caused by Percutaneous Intravascular Devices
303 Nosocomial Pneumonia
304 Nosocomial Urinary Tract Infections
305 Nosocomial Hepatitis and Other Infections Transmitted by Blood and Blood Products
306 Human Immunodeficiency Virus in Health Care Settings
307 Nosocomial Herpesvirus Infections

Section B. Infections in Special Hosts

308 Infections in the Immunocompromised Host: General Principles
309 Prophylaxis and Empirical Therapy of Infection in Cancer Patients
310 Risk Factors and Approaches to Infections in Transplant Recipients
311 Infections in Hematopoietic Stem Cell Transplant Recipients
312 Infections in Solid Organ Transplant Recipients
313 Infections in Patients with Spinal Cord Injury
314 Infections in the Elderly
315 Infections in Asplenic Patients
316 Infections in Injection Drug Users
317 Postoperative Infections and Antimicrobial Prophylaxis

Section C. Surgical and Trauma-Related Infections

318 Infections in Patients with Burns
319 Bites

Section D. Immunization

320 Immunization

Section E. Biodefense

321 Bioterrorism: An Overview
322 Plague as an Agent of Bioterrorism
323 Tularaemia as a Bioterrorism Weapon
324 Smallpox as an Agent of Bioterrorism
325 Anthrax as an Agent of Bioterrorism
326 Botulism Toxin as an Agent of Bioterrorism
327 Viral Hemorrhagic Fevers as Agents of Bioterrorism

Section F. Zoonoses

328 Zoonoses

Section G. Protection of Travelers

329 Protection of Travelers
330 Infections in Returning Travelers
OH, MY GOD!
THERE ARE BILLIONS
OF THEM!

OF WHAT DOCTOR?!
BILLIONS OF WHAT?!
Parasite-Host Relationship
SUPPORT BACTERIA!

it's the only culture some people have
Otherwise harmless germs can be opportunists

Taking advantage of a weakened host condition
Why Fever?
Dipsosaurus dorsalis
Function of Fever

Courtesy of the American Museum of Natural History.
10 Plagues

1. Water to blood
2. Frogs
3. Lice
4. Flies
5. Animals died from disease
6. Boils
7. Hail
8. Locusts
9. Darkness
10. Death of firstborn

Exodus 7-12

GREG CAN'T PLAY MUMPS
1. Virus infects body, cells display viral antigens.

2. Macrophages engulf virus and display viral antigen.

3. Macrophages activate helper T cells.

4. Helper T cells activate cytotoxic T and B cells.

5. B cells form plasma cells.

6. Plasma cells make antibodies which bind to viral antigen.

7. Antibodies attach to the virus and infected body cells, signals for their destruction.

8. Cytotoxic T cells destroy infected body cells.
**HUMORAL IMMUNITY**

- Extracellular microbes (e.g., bacteria)
- B lymphocytes
  - Secreted antibody
  - Neutralization
  - Lysis (complement)
  - Phagocytosis (PMN, macrophage)

**CELLULAR IMMUNITY**

- Intracellular microbes (e.g., viruses)
- Antigen-presenting cell
  - Helper T cell
  - T-cell receptor
  - Processed and presented antigen
  - Cytokines
  - Proliferation and activation of effector cells (cytotoxic T cells, natural killer cells, macrophages)
  - Lysis of infected cell

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Antigen produces antibody
THE NEXT TO GO

FIGHT TUBERCULOSIS!
Red Cross Christmas Seal Campaign
Cavities open into the bronchi, allowing spread of *M. tuberculosis* through coughing.

90–95% of infected individuals.

5–10% of infected individuals.

Haematogenous spread: *M. tuberculosis* DNA detected in tissues by *in situ* PCR.

Reactivation of TB: for example, after immunosuppression, HIV infection or smoking.

Progression to cavitary TB.

Copyright © 2005 Nature Publishing Group

*Nature Reviews* | *Immunology*
Natural history of TB infection

4-6 weeks:
- Exposure
- Infection
- Dendritic Cell (innate response)
- T Cell (adaptive response)
- Initial immune control of bacteria
- Inability to control bacteria
- Elimination of bacteria

Years-decades:
- Granuloma
- Elimination of bacteria
- Reactivation
- Lifelong containment
- Onward transmission
- Active TB
- Latent TB

Active TB
White Blood Cell Lineages

Bone Marrow
- hematopoietic stem cell
- common lymphoid progenitor
- common myeloid progenitor

Thymus
- B cell
- T cell

Blood
- neutrophil polymorphonuclear
- monocyte
- immature dendritic cell

Tissue
- macrophage
- immature dendritic cell

Lymph Node
- mature dendritic cell
Immune system

Acquired

- T-cell immunity (cell-mediated immunity)
  - Whole T-cells released into:
    - Suppressor T-cells
    - Helper T-cells
    - Cytotoxic T-cells
    - Death of the body's cells that are infected with a virus or otherwise damaged

- B-cell immunity (humoral immunity)
  - Antigen exposure
    - Lymphoblasts
    - Plasma cells
      - Antibodies
      - Complement cascade
        - Classical pathway
      - Complement cascade
        - Alternative pathway
    - Clonal B-cells
      - Memory B-cells

Innate

- Bloodbourne
  - Complement cascade
    - Phagocytes
      - Neutrophils
      - Macrophages
      - Basophils
      - Eosinophils
      - Natural killer cells
    - Death of dangerous organisms
    - Direct killing of bacteria

- Physical barriers
  - 1. Skin
  - 2. Mucous membranes
  - 3. Saliva
  - 4. Flushing action of urine and tears
  - 5. Stomach acid
  - Stops infection before it enters the body

virtualmedicalcentre.com®
• inflammatory response to infection
Murphy’s Law

“If anything can go wrong, it will”
SEPTIC SHOCK

depth rapid breathing

burns

peritonitis

septic abortion

catheter

warm bounding pulse
• inflammatory response to infection
• inflammatory response to infection overshoots sepsis
The first time the allergy-prone person runs across an allergen such as ragweed,

he or she makes large amounts of ragweed IgE antibody.

These IgE molecules attach themselves to mast cells.

The second time that person has a brush with ragweed,

the IgE-primed mast cell will release its powerful chemicals,

and the person will suffer the wheezing and/or sneezing, runny nose, watery eyes, and itching of allergy.
ALLERGIC REACTIONS

Skin Contact
- poison plants
- animal dander
- pollen
- latex

Injection
- bee sting
- medication

Ingestion
- medication
- nuts & shellfish

Inhalation
- pollen
- dust
- mold & mildew
- animal dander
• inflammatory response to infection
• inflammatory response to infection overshoots _sepsis
• inflammatory response to a non-infection _ allergy
Clinical Manifestations of Acute Rheumatic Fever

- Polyarthritis
- Carditis
- Erythema Marginatum
- Chorea
- Subcutaneous nodules

Timeline in months:
- 0
- 1
- 2
- 3
- 4
- 5
- 6
Antibiotics don't work on colds...
...or most coughs and sore throats.

Not my thing, know what I mean?...
• inflammatory response to infection
• inflammatory response to infection overshoots _sepsis
• inflammatory response to a non-infectious entity _ allergy
• inflammatory response to infection cross-reacts _ rheumatic fever
David Vetter
1971-84
<table>
<thead>
<tr>
<th>Site</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacteria</td>
<td>T-cell deficiency</td>
</tr>
<tr>
<td></td>
<td>N-K cell defect</td>
</tr>
<tr>
<td></td>
<td>IL-12</td>
</tr>
<tr>
<td>Encapsulated organisms</td>
<td>B-cell or complement deficiency</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenza</em>, <em>Nisseria</em></td>
<td></td>
</tr>
<tr>
<td>Catalase-positive organisms</td>
<td>Neutrophil/phagocyte defects (CGD)</td>
</tr>
<tr>
<td><em>Staph aureus</em>, <em>Klebsiella</em>, <em>Serratia</em></td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td>T-cell deficiency</td>
</tr>
<tr>
<td>Herpes, varicella, CMV</td>
<td>IL-12/ NK cell defects</td>
</tr>
<tr>
<td>Enteroviruses (echovirus, Coxsackie)</td>
<td>B-cell deficiency</td>
</tr>
<tr>
<td>Fungi</td>
<td>T-cell deficiency</td>
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<tr>
<td><em>Candida</em></td>
<td>T-cell or phagocyte defects</td>
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<td><em>Aspergillus</em></td>
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<tr>
<td>Parasites</td>
<td>B-cell deficiency</td>
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<tr>
<td><em>Giardia lamblia</em></td>
<td>T-cell deficiency</td>
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<td><em>Toxoplasma gondii</em></td>
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<td>Opportunistic infections</td>
<td>T-cell deficiency</td>
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<tr>
<td><em>Pneumocystis carinii</em></td>
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<tr>
<td><em>Cryptosporidium</em></td>
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</tbody>
</table>
• inflammatory response to infection
• inflammatory response to infection overshoots _sepsis
• inflammatory response to a non-infectious entity _ allergy
• inflammatory response to infection cross-reacts _ rheumatic fever
• inflammatory response absent _ primary immunodeficiency
Al McGuire 1928-2001
• inflammatory response to infection
• inflammatory response to infection overshoots _sepsis
• inflammatory response to a non-infectious entity _ allergy
• inflammatory response to infection cross-reacts _ rheumatic fever
• inflammatory response absent _ primary immunodeficiency
• inflammatory response weakened by disease _ leukemia
Rock Hudson
1925-85
Opportunistic Diseases of AIDS

- Candidiasis of bronchi, trachea, esophagus, or lungs
- Invasive cervical cancer
- Coccidioidomycosis
- Cryptococcosis
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (particularly CMV retinitis)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, multiple forms
- Mycobacterium avium complex
- Tuberculosis
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV
Targets for HIV Meds

- Protease
- Virus attaches to cell
- Virus fuses to cell
- Virus enters cell
- Reverse transcriptase
- Integrase
- Healthy Cell (CD4)
- Infected cell produces new virus
GREAT TO SEE YOU!
GIVE US A BIG HUG!!

Doctors without Boundaries
• inflammatory response to infection
• inflammatory response to infection overshoots_sepsis
• inflammatory response to infection cross-reacts_rheumatic fever
• inflammatory response to a non-infectious entity_allergy
• inflammatory response absent_primary immunodeficiency
• inflammatory response weakened by disease_leukemia
• inflammatory system attacked by an infection_HIV, AIDS
– Eleanor Roosevelt
1884-1962
"Buck, are you sure that guy who gives you the steroids is giving you the right stuff?"
- inflammatory response to infection
- inflammatory response to infection overshoots _sepsis
- inflammatory response to a non-infectious entity _ allergy
- inflammatory response to infection cross-reacts _ rheumatic fever
- inflammatory response absent _ primary immunodeficiency
- inflammatory response weakened by disease _ leukemia
- inflammatory response weakened by infection _ AIDS
- inflammatory response weakened medically _ anti-inflammatories
Tissues of The Body Affected By Autoimmune Attack

Triggers
1. Stress
2. Hormones
3. Metals
4. Food Antigens
5. Pesticides & Piolons

Thyroid
Hashimoto's Thyroiditis
Graves Disease

Blood
Leukemia
Lupus
Hemolytic Dysgammaglobulinemia

GI Tract
Celiac
Chronic's Disease
Ulcerative Colitis

Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Lungs
Asthma
Wegener's Granulomatosis

Brain
Multiple Sclerosis
Guillain-Barré Syndrome
Psychological

Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

Muscles
Fibromyalgia
Muscular Dystrophy

Skin
Eczema
Psoriasis
Scleroderma
Vitiligo

Autoimmune Disorder
## The spectrum of autoimmune disease

### Organ Specific Autoimmune Diseases

- Graves Disease
- Hashimoto Thyroiditis
- Diabetes Type I
- Goodpasture Syndrome
- Pernicious Anemia
- Primary Biliary Cirrhosis
- Myasthenia Gravis
- Dermato-/Polyomyositis
- Vasculitis
- Rheumatoid Arthritis
- MCTD
- Scleroderma
- SLE

### Multi-systemic Autoimmune Diseases

- Thyroid: TSHR Abs, TPO Abs
- Thyroid: TPO Abs, Tg Abs
- Pancreas: GAD II Abs, IA2 Abs, ICA
- Kidney: GBM Abs
- Stomach: Parietal Cell Abs
- Liver, Bile: AMAbs
- Muscles: AChR Abs
- Skin / Muscles: Jo 1 Abs
- Vessels: ANCA
- Joints: CRP, RF, RA33 Abs, Sa Abs
- RNP Abs
- Sci 70 Abs, CENP Abs, PM-Scl Abs
- ANA, Cardiolipin Abs, Beta 2 GP I Abs
Acute Disseminated Encephalomyelitis (ADEM)
Alopecia Areata
Addison’s Disease
Ankylosing Spondylitis
Antiphospholipid Antibody Syndrome (APS)
Autoimmune Hemolytic Anemia
Autoimmune Hepatitis
Autoimmune Inner Ear Disease
Bullous Pemphigoid
Coeliac Disease
Chagas Disease
Crohn’s Disease
Dermatomyositis
Endometriosis
Guillain-Barre Syndrome
Graves’ disease
Goodpasture’s Syndrome
Hashimoto’s Disease
Hidradenitis Suppurativa
Interstitial Cystitis
IgA Nephropathy
Idiopathic Thrombocytopenic Purpura
Kawasaki Disease
Lupus Erythematosus
Morphea

Mixed Connective Tissue Disease
Myasthenia Gravis
Multiple Sclerosis (MS)
Narcolepsy (possibly)
Neuromyotonia
Opsoclonus Myoclonus Syndrome (OMS)
Psoriasis
Primary Biliary Cirrhosis
Pernicious Anemia
Polymyositis
Psoriatic Arthritis
Pemphigus Vulgaris
Rheumatoid Arthritis
Scleroderma
Stiff Person Syndrome
Sjögren’s Syndrome
Schizophrenia
Temporal Arteritis
Ulcerative Colitis
Vasculitis
Vitiligo
Wegener’s Granulomatosis
Laurence Olivier
1907-1989
• inflammatory response to infection
• inflammatory response to infection overshoots _ sepsis
• inflammatory response to infection cross-reacts _ rheumatic fever
• inflammatory response to a non-infectious entity _ allergy
• inflammatory response absent _ primary immunodeficiency
• inflammatory response weakened by disease _ leukemia
• inflammatory response weakened by infection _ AIDS
• inflammatory response weakened medically _ anti-inflammatories
• inflammatory response against self _ autoimmune disorders
• inflammatory response against self _ muscle
**Normal Muscle**

- border of muscle bundle (fascicle)
- normal muscle fibers
- blood vessel

When normal muscle fibers are viewed under a microscope, they look like puzzle pieces that fit together neatly.

**Polymyositis**

- inflammatory cells
- invasion of fibers by inflammatory cells

In polymyositis, inflammatory cells of the immune system invade previously healthy muscle cells, which become rounded and variable in size.

**Inclusion-Body Myositis**

- inclusion bodies
- vacuoles

Inclusion-body myositis is characterized by muscle fibers that contain empty, bubble-like spaces (vacuoles) and clumps of cellular material (inclusion bodies). Inflammatory cells can be seen between the fibers.

**Dermatomyositis**

- shrinkage (atrophy) of fibers near border of fascicle
- inflammatory cells around fascicle and between fibers
- cuff of inflammatory cells around blood vessel

In DM, inflammatory cells are concentrated around blood vessels at the borders of the muscle fiber bundles (fascicles), and fibers in this region often shrink. Inflammatory cells can sometimes be seen forming a cuff around blood vessels.
<table>
<thead>
<tr>
<th>Medication or treatment</th>
<th>How it works</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>corticosteroids</strong></td>
<td>Dampens inflammation and immune response by interfering with processing of antigens and with early triggering of T cell and B cell production and later proliferation of B cells and T cells. These cells are produced by the immune system in autoimmune diseases such as PM and DM.</td>
<td>Can be taken orally as prednisone and related compounds; also available for intravenous use. Many side effects with long-term, high-dose therapy, such as weight gain and redistribution of fat to face, abdomen and upper back; thinning of skin; susceptibility to infection; bone loss; muscle damage; cataracts; elevated pressures in eyes (glaucoma); psychological disturbances; high blood pressure; high blood sugar; growth slowing in children.</td>
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<tr>
<td>prednisone tablets</td>
<td></td>
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<tr>
<td>(Deltasone)</td>
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<tr>
<td>intravenous methylprednisolone sodium succinate (Solu-Medrol)</td>
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<tr>
<td><strong>azathioprine</strong></td>
<td>Interferes with proliferation of B cells and T cells.</td>
<td>Can suppress production of several types of blood cells, so cell counts must be monitored; increases risk of cancer.</td>
</tr>
<tr>
<td>(Imuran)</td>
<td></td>
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<tr>
<td><strong>methotrexate</strong></td>
<td>Interferes with proliferation of B cells and T cells.</td>
<td>Can cause liver damage; used in higher doses to treat cancer.</td>
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<tr>
<td>(Rheumatrex, Folex, Mexate)</td>
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<td><strong>cyclosporine</strong> (Neoral, Sandimmune)</td>
<td>Keeps T cells from stimulating production of more T cells and B cells (&quot;upstream&quot; of azathioprine and methotrexate action).</td>
<td>Doesn’t affect production of cells other than T cells and B cells; can cause kidney damage, infection, high blood pressure, tremor and excessive hair growth.</td>
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<td><strong>cyclophosphamide</strong> (Cytoxan)</td>
<td>Interferes with proliferation and activity of B cells and T cells</td>
<td>Also used in cancer; toxic to many kinds of cells, including those of the blood and bladder; can cause sterility in both sexes.</td>
</tr>
<tr>
<td><strong>mycophenolate mofetil</strong> (CellCept)</td>
<td>Interferes with proliferation of B cells and T cells.</td>
<td>Can cause diarrhea, vomiting, infection (particularly with cytomegalovirus); increases risk of cancer, especially lymphomas; causes depletion of certain blood cells.</td>
</tr>
<tr>
<td><strong>tacrolimus</strong> (Prograf, old name FK506)</td>
<td>Keeps T cells from stimulating production of more T cells and B cells (&quot;upstream&quot; of azathioprine and methotrexate action).</td>
<td>Can damage kidneys; can cause headaches, tremors and sleep difficulties; diarrhea, nausea and vomiting; high blood pressure, high blood sugar and high blood levels of potassium; increases risk of infection and lymphomas. Drug breakdown interfered with by grapefruit juice; potential for kidney damage increased by some anti-inflammatory drugs.</td>
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<td>hydroxychloroquine sulfate (Plaquenil)</td>
<td>Mechanism not understood; used in arthritis, lupus, malaria; can be used to reduce steroid dosage in myositis, particularly in children.</td>
<td>Can treat muscle symptoms and dermatomyositis rash; can cause damage to eyes’ retinas or corneas; regular eye exams needed.</td>
</tr>
<tr>
<td>infusion of mixed immunoglobulins; IVlg (Gammar, Gammagard, Sandoglobulin others)</td>
<td>Has complex actions on immune system, such as providing antibodies against patient’s own antibodies; interfering with immune system reaction to antibody-marked cells; interfering with blood-transported chemicals released by immune system; interfering with activation and maturation of T cells and B cells.</td>
<td>Doesn’t affect production of cells other than T cells and B cells; can cause kidney damage, infection, high blood pressure, tremor and excessive hair growth.</td>
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<td>plasmapheresis</td>
<td>Removes antibodies and proteins made by the immune system from the blood and returns “cleansed” blood to patient.</td>
<td>Very rarely used in myositis since 1992 study showed it was no more effective than placebo; some think it’s useful when combined with immunosuppressant drugs.</td>
</tr>
</tbody>
</table>
I slept through the class in med school about your condition, but I'm catching up now... be with you in a few minutes!
“You’re just going to feel a little pinch, then a horrific burning pain, your eyes will roll back into your head, you will drool uncontrollably...”