Effect of Aging (and Frailty) on the Clinical Manifestations of Infections

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  – Editorial Board: Journal of the American Geriatrics Society
  – Associate Editor, Hazzard’s *Geriatric Medicine and Gerontology, 6th and 7th editions*
  – Contributor/Author: *UpToDate*
Agenda

• Why study aging?
  – What are the benefits?

• Age and altered manifestations of classic infections
  – Fever
  – “Classic Sxs” - Examples: Bacteremia, TB

• Frailty and Infection – reciprocal relationships and plausible mechanisms

• OAIC/CFAR R24 in HIV/Aging
“Life would be infinitely happier if we could only be born at the age of eighty and gradually approach eighteen.”

Mark Twain
“Age is a question of mind over matter. If you don’t mind, it doesn’t matter.”

Satchel Paige
Non-aging survival curve for a wild animal

Risk of death same every year (50:50)
Animals do not appear to show signs of aging
Don’t live long enough in wild

Why?
- Predation
- Disease
- Habitat
- Starvation
- Accidental death

MULTIPLE SLIDE

Slide courtesy of Neal Fedarko
As humans have increasingly controlled their environment, their life expectancy has ↑ dramatically (“Rectangularization” of the survival curve).
"Rectangularization" of the Survival Curve:

<table>
<thead>
<tr>
<th>Transition</th>
<th>Major Factors in Transition</th>
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<tbody>
<tr>
<td>A-B</td>
<td>Improved housing, sanitation, antiseptics</td>
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<tr>
<td>B-C</td>
<td>Public health, hygiene, immunization</td>
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<tr>
<td>C-D</td>
<td>Antibiotics, improved medical practice, nutrition, health education</td>
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<tr>
<td>D-F</td>
<td>Recent biomedical breakthroughs</td>
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</table>

Figure 1.5
Human survival curves from ancient times through the twentieth century. The curve representing the 1990s is essentially the same as that of the 1970–1980 decade on this scale. Note the transition from an almost linear decline in survivorship with age in ancient times, to the large bulge of the curves of recent years. The logical extension of this “bulge” of the curve is to become a right angle (see text).
The Goal of Aging Research: A New Kind of Old Person

Slide courtesy of Jeff Halter

Normal person, age 70 ➔ Normal person, age 114
Aging Research: Biggest Bang For the Buck?

- Just Like Today - average 50 year old woman lives to 81
- Cure Cancer Today
- Cure Heart Disease Today
- Cure Cancer and Heart Disease Today
- Slow Down Aging

[The amount diet restriction produces in rats; first published in 1935]

Years of Life Left at Age 50

30  40  50  60  70  80

Slide courtesy of Jeff Halter
"Rectangularization" of the Survival Curve:

**Figure 1.5**

Human survival curves from ancient times through the twentieth century. The curve representing the 1990s is essentially the same as that of the 1970-1980 decade on this scale. Note the transition from an almost linear decline in survivorship with age in ancient times, to the large bulge of the curves of recent years. The logical extension of this "bulge" of the curve is to become a right angle (see text).
Figure 1.2a  Percentage of Medicare FFS Beneficiaries by Number of Chronic Conditions: 2010

Figure 2.1 Percentage of Medicare FFS Beneficiaries by Number of Inpatient Admissions and Number of Chronic Conditions: 2010

DATA HIGHLIGHTS:
As the number of chronic conditions increased so did hospitalizations:

- Only 4% of beneficiaries with 0 or 1 chronic condition were hospitalized and less than 1% were hospitalized 3 or more times during the year.
- Almost two-thirds of beneficiaries with 6 or more chronic conditions were hospitalized and 16% had 3 or more hospitalizations during the year.
Figure 3.1a  Per Capita Medicare Spending for Medicare FFS Beneficiaries by Number of Chronic Conditions: 2010

Average spending for Medicare FFS beneficiaries: $9,738

- 0 to 1 chronic conditions: $2,025
- 2 to 3 chronic conditions: $5,698
- 4 to 5 chronic conditions: $12,174
- 6+ chronic conditions: $32,658
83 years old; HTN, Hyperlipidemia, prior MI

83 years old; HTN, Hyperlipidemia, prior MI
“You’re looking old Indy . . .” Marian

“It’s not the years, Honey, it’s the mileage . . . . . .” Indiana Jones
Rates of invasive pneumococcal disease by age-group, United States

Cases per 100,000 pop per year

www.cdc.gov/abcs

Risk of Serious Pneumococcal Disease is Increased by Co-Morbidity at all ages

“Immune” Deficits in the Elderly

- Comorbidity (COPD)
- Comorbidity (CHF)
- Comorbidity (CRI)
- Comorbidity (Diabetes)
- Comorbidity (PVD)
- Comorbidity (Dementia)

- Social Factors
  - Nutrition
  - Nursing Home
  - Access to Care
    - Financial
    - Geographic
    - Transportation

- Immune Senescence
Typical Epidemiologic Model for Infectious Diseases

- **Koch’s Postulates**
  - Agent is present in the disease
  - The disease is never present without the agent
  - The agent reproduces the disease in an appropriate animal model and can be re-isolated
Multiple Risk Factor Model For Pneumonia Susceptibility in the Elderly\textsuperscript{1}

**Host Factors**
- Comorbidity
  - Alcoholism RR 9.0
  - Asthma RR 4.2
  - Heart Disease RR 1.9

**Medication Use**
- Impaired ADLs/Cognition
- Impaired Cough/Gag Reflex
- Immune ‘Senescence’

**Poor Nutrition**

**Social Factors**
- Crowding/Nursing Home
- Poor Understanding/Acceptance of Prevention

\textsuperscript{1}Ely W, Inf in Med, 1999 and Loeb M. Clin Inf Dis; 2004
Age-related changes in physiology alter presentation of infectious disease in seniors
Redefinition of Fever

- Peak temperatures fall about 0.1-0.2°C per decade over the age of 30
- By age 80, the mean temperature is about 1°C lower

Definition of Fever in Elderly, Debilitated Adults*

- Study in NH patients by Castle, et al*
- Sensitivity and Specificity using three different thresholds
- Redefine fever in frail elderly as:
  - $\geq 99^\circ F$ po or $99.5^\circ F$ pr (repeated measures)

Changes in Clinical Presentation with Acute Infection
Example: Bacteremia

Age-related differences in symptoms, diagnosis and prognosis of bacteremia

Astrid L Wester¹, Oona Dunlop², Kjetil K Melby³, Ulf R Dahle¹ and Torgeir Bruun Wyller³,⁵
Comorbidities by age group in bacteremic adults

Wester et al. BMC Infectious Diseases 2013, 13:346
http://www.biomedcentral.com/1471-2334/13/346
**Classic Sxs:** fever/chills, local pain, N/V, diarrhea, cough, dyspnea, sputum, urgency, hematuria, pyuria, rash, coma, seizures

**Atypical Sxs:** malaise, fall, dizziness, syncope, immobility, acute incontinence, paresis, confusion, difficulty speaking

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Wester et al. *BMC Infectious Diseases* 2013, 13:346
http://www.biomedcentral.com/1471-2334/13/346
Predictors of Organ Failure

OR on Multivariate Analysis

- WBC < 3000: 4.16
- Tachypnea: 3.86
- Dailly steroids: 2.75
- Declining Function: 2.28
- Age > 65: 1.65
- Tachycardia: 1.5
- comorbid illnesses: 1.19
- classic Sxs: 0.67

Wester et al. BMC Infectious Diseases 2013, 13:346
http://www.biomedcentral.com/1471-2334/13/346
Many examples of lower incidence of “classic” Sx’s in old vs. young adults

- **Pneumonia**
  - Less cough, fever, leukocytosis
  - More tachypnea (due to increased residual volumes in aged lungs?), confusion/delirium, change in eating habits, altered mental status

- **UTI**
  - Less fever, flank pain, leukocytosis
  - More confusion/delirium, altered mental status
CRP as a predictor of bacterial infection

- Because other predictors of bacterial infection perform poorly in seniors, biomarkers examined
- CRP > 60 mg/l demonstrated good predictive value in Australian seniors in the ER
Changes in Clinical Presentation, Chronic Infection Example: TB
Presenting Symptoms by Age Group - Canada

Presenting Symptoms by Age Group - HK

Chan CHA, et al. Tubercle Lung Disease 1995; 76:290-4

Non-specific = dizziness, abd pain, “mental dullness”
“Meta-Analysis” of Pulmonary TB in Younger vs. Older Adults*

Clinical Features

Tuberculin Skin Test and Radiographic Findings by Age Group - Canada

**Microbiologic and Radiographic Findings by Age Group - HK**

*Chan CHA, et al. Tubercle Lung Disease 1995; 76:290-4*
“Meta-Analysis” of Pulmonary TB in Younger vs. Older Adults*

Summary of Diagnostic and Laboratory Differences by Age in Patients with TB

• Clinical
  – Older adults → LESS fever, sweating or hemoptysis
  – Older adults → MORE dyspnea

• Diagnostic
  – Older adults → LESS cavitation and TST positivity
  – Older adults → MORE AFB positive sputum smears/Cx

• Laboratory
  – Older adults → LESS leukocytosis
  – Older adults → MORE hypoalbminemia

Reciprocal relationships between frailty and infection:

Lessons from pneumonia and influenza...
Many definitions of frailty/impaired function

- **Fried Frailty Phenotype (FFP)** - slowness, weakness, shrinking, inactivity, exhaustion
  - 1-2 “pre-frail”, 3+ frail
- **Rockwood** - accumulated deficits/decreased reserve
  - Count number of conditions/lab abnormalities
- **Short Physical Performance Battery** - walking speed, chair stand, balance test

**Barthel Index** = score in 10 ADLs; 100=totally independent, 0= totally dependent

**HARP Index** = hospital adm risk profile – age, MMSE score, IADL measures

**Charlson Index** = scores 1-6 on 18 medical illnesses to assess co-morbidity

**Pneumonia Severity Index** = mortality predictive index for pneumonia based on historical variables and acute illness variables
Is frailty linked to poor influenza vaccine responses? Yes

**Screening:**
- Age: > 70 yrs
- Frailty screening
- Community-dwelling
- Exclusions

(N=94 screened) 
(N=78) 
(N=71)

**Timeline**
- Early October, 2007
- Early - mid November, 2007

2007 – 2008 influenza season

**Visit 1:**
- History & physical
- Blood draw
- Vaccine administration

**Visit 2:**
- 3-4 wks after Visit 1
- Brief history
- Blood draw

*Fig. 1. Pre-vaccination screening and blood draw, TIV immunization, as well as post-vaccination GMT ratios.*
PPS vax response declines with age (-----) and frailty (-----) almost linear from age 65 to 85: severe frailty about = to aging 10 yrs

I. Ridda et al. / Vaccine 27 (2009) 1628–1636
Is risk of influenza linked to frailty?

Yes

**Fig. 1.** Pre-vaccination screening and blood draw, TIV immunization, as well as post-vaccination blood draw and influenza surveillance.
Is pneumonia risk linked to frailty?

Yes

JAGS 57:882–888, 2009

- 1173 seniors (65-94 yrs) with PNA
- 2346 age-, sex-matched controls

- Pneumonia \(\rightarrow\) ICD9 code
  - Confirmed by review of radiology reports and medical record

- Independent predictors of PNA risk:
  - Presence/severity of:
    - Cardiovascular disease (CHF > non-CHF)
    - Lung Disease
  - Low weight or recent weight loss
  - Poor Activities of Daily Living (ADL) functional status
Is pneumonia severity linked to functional status and frailty? Yes

Even at the extreme of frailty, NH residence, degree of frailty predicts infection risk, and...

Bula, et al. JAGS, 2004;52:700-706
Infection “dose” predicts functional decline

![Bar chart showing the percentage of residents with functional decline](image)

- **No infection**
- **1 infection**
- **2 or more infections**

**0–3 months**
- No infection: 16.4%
- 1 infection: 22.4%
- 2 or more infections: 27.0%

**3–6 months**
- No infection: 20.0%
- 1 infection: 28.2%
- 2 or more infections: 31.1%

*P = .001*  
*P < .001*

*Mantel-Haenszel test for trend*

Does frailty alter outcomes after PNA? Yes

Does the severity of PNA increase the risk of frailty?

- 30-day mortality predicted by:
  - Functional status (Barthel Index)

- 18-month mortality predicted by:
  - Functional status
  - Frailty (HARP index)

- Functional decline predicted by:
  - Pneumonia severity index

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Barthel Index = score in 10 ADLs; 100=totally independent, 0=totally dependent

HARP Index = hospital adm risk profile – age, MMSE score, IADL measures

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Pneumonia Severity Index = mortality predictive index for pneumonia based on historical variables and acute illness variables
Infection as a trigger of disability/frailty

Moving beyond the associations . . . . . are there plausible mechanisms?

Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination

Liam Smeeth, Ph.D., Sara L. Thomas, Ph.D., Andrew J. Hall, Ph.D., Richard Hubbard, D.M., Paddy Farrington, Ph.D., and Patrick Vallance, M.D.

Risk of MI and Stroke after acute respiratory or urinary tract infections

- UK General Practice Research Database
  - > 5 million subjects
  - Examined 20,486 persons with first MI and 19,063 persons with first stroke
  - Examined risk of MI or stroke after flu, pneumococcal or tetanus vaccine OR after acute respiratory illness or urinary tract infection (UTI)
Do vaccines or illness increase the risk of MI?

No . . . and Yes

Days after:

- 1-3
- 4-7
- 8-14
- 15-28
- 29-91

RR

*
Do vaccines or illness increase the risk of stroke?  

No . . . and Yes

<table>
<thead>
<tr>
<th>Days after:</th>
<th>1-3</th>
<th>4-7</th>
<th>8-14</th>
<th>15-28</th>
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What’s the mechanism? Perhaps, the inability to shut down inflammation in advanced age.

Microbiologically confirmed *S. pneumoniae* infection (invasive disease (+ BC) in 60%, rest with pneumonia)
Prolonged response after endotoxin injection

Changes in body temperature

<table>
<thead>
<tr>
<th>Hours after endotoxin administration</th>
<th>Elderly</th>
<th>Young</th>
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<td>8</td>
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Δ°C
Prolonged response after endotoxin injection
Greater effect on target organs (e.g. liver → increases CRP)
Inflammation in the Aged Phenotype

Infection

Inflammation

Time

Young Adult
Aged Adult
Conclusions: Acute Infection and Frailty

- Frailty carries an increased risk of infection, serious infection, and predicts mortality after infection.
- Acute infection increases the risk of major disabling illnesses like MI and stroke.
  - Increased risk of functional decline in the post-infection period.
- Reciprocal relationship is even apparent in NH residents despite concerns of “floor effect”.
- Mechanism may be acute inflammation AND inability to shut it down...
Summary

• Older adults more likely to get infected, suffer serious infection and mortality due to infection vs. young adults

• Age-related and Co-morbid illness-related changes in physiology alter presentation of infection in seniors
  – True for acute and chronic infections

• Frailty is both a risk factor for and outcome of infection
Shameless plug for a new pilot program . . . . . .
Developing Research at the Interface of HIV and Aging

- R24 AG044325
- Kevin High and Alan Landay PD/PI’s
  - Michael Saag, Michael Miller, Heidi Crane CoI’s
- Collaboration of CFARs and Older Americans Independent Centers (OAICs)
  - Funded 9/1/13
OAICs ("Pepper" Centers)
CFARs
Specific Aims
R24 AG044325

1. Harmonize data collection for functional/disability measures across CFARs and OAICs
   - Data Harmonization Workshops to select measures to be piloted for routine collection

2. Validate key instruments of functional outcomes and geriatric phenotypes in senior population (>65) and HIV+ subjects (>50)
Specific Aims
R24 AG044325 cont’d

3. Support pilot projects interfacing HIV and Aging

4. Identify and mentor junior faculty

5. Disseminate information to the fields of HIV and geriatrics
Three Types of Pilot Studies

• Classical pilot grants: awarded annually at $20,000/grant from the R24 with a 1:2 match by the home CFAR or OAIC (total award $30,000)

• Reverse match: will provide a “reverse match” to CFARs or OAICs that award a pilot application focused on HIV/Aging at a 1:2 ratio up to $10,000

• Rapid cycle pilots: $1000-$5000 trigger funds that can be used for specific analyses of stored samples, or rapid accumulation of key data anticipated to lead to an extramural pilot application (R03 or R21)
Questions?