Controversies in Geriatric Medication Management
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Topics
- Renal function estimation for drug dosing
- Acute delirium and antipsychotics
- Hip fractures and bisphosphonates

Renal Function Estimation for Drug Dosing

Which equation (Cockcroft-Gault vs. MDRD) should be used?
Case Study #1

- 90 yo female with CAD, HTN, and asthma admitted with LLE cellulitis.
- Wt=56 kg  Ht=62 in  SCr=0.85

What dose of vancomycin should you start?
A. 1 gm IV Q24H  
B. 1 gm IV Q12H  
C. 1 gm IV Q8H

Renal Function in the Elderly

- Impaired renal function is common in the elderly
  - Age-related decline in glomerular filtration rate (GFR) and tubular function
  - A normal serum creatinine (SCr) might be present despite renal impairment
    - "Concealed renal insufficiency"
    - Reduced creatinine production due to decreased muscle mass
    - Increase risk for adverse drug reactions (ADRs) from lack of dose adjustments for renally cleared medications

SCr Assay and GFR Equation Development
Cockcroft-Gault (CG) Equation
- Estimation of creatinine clearance (CrCl)
  - Two 24-hour urine collections obtained in 249 adult men
  - Linear regression
  - Mean age = 56.8 years (range 18-92)
  - Mean weight = 72 kg
  - Mean SCr=1.4 mg/dL (CrCl = 73 ml/min)

Modification of Diet in Renal Disease (MDRD) Equation
- Estimation of glomerular filtration rate (GFR) = MDRD-6
  - Stepwise regression analysis
  - Measured GFR by renal clearance of 125I-iodotamate
  - 1628 study patients with CKD
    - Mean age 50.6±12.7 years (range 18-70)
    - 60% Male
    - Mean weight = 79.6±16.8 kg
    - Mean SCr = 2.3 mg/dL (GFR = 48.6 ml/min/1.73 m²)
- Simplified formula published in 2000 = MDRD-4
  - Excluded urine urea nitrogen, albumin, and blood urea nitrogen
  - Revised for use with new SCr assay in 2005

Which Equation to Use?
- NKDEP statement (September 2009):
  - Recommended utilizing either MDRD or CG equation for drug dosing
  - Based on study by Stevens et al. (2009) comparing both equations to measured GFR of 5,504 pts
    - Found 11-29% difference between MDRD and CG equations
    - Study conclusion: MDRD equation had the greatest concordance with measured GFR for both staging and adjustment of drug dosing.
Which Equation to Use? (cont.)

- **Limitations** to study by Stevens et al.:
  - Simulation rather than actual clinical outcomes
  - Comprised of early-onset CKD pts (including some from original MDRD study)
  - 87% pts under 65 yo
  - MDRD equation needs to be converted to the BSA-adjusted GFR values (ml/min) which is often not done in clinical practice

- Significant variations exists between the MDRD and CG equations
  - 21-60% difference in dosing of selected medications between the 2 equations found in several studies
  - Estimated GFR from MDRD equation is consistently higher than that from CG equation

Data in the Elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (yr)</th>
<th>SCr (mg/dl)</th>
<th>Wt (kg)</th>
<th>Method</th>
<th>CG-CrCl (ml/min)</th>
<th>MDRD-CrCl (ml/min)</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Den Noortgate et al.</td>
<td>2002</td>
<td>48</td>
<td>35% male</td>
<td>84.4 ± 6.3</td>
<td>Cr EDTA clearance</td>
<td>51.5 ± 19.2</td>
<td>68.7 ± 28.2</td>
<td>No significant difference found between the studied formulas. CG underestimates GFR when GFR &gt; 60 ml/min while MDRD slightly overestimates GFR in the elderly</td>
<td>CG useful for elderly with moderate to severe renal impairment</td>
</tr>
<tr>
<td>Lamb et al.</td>
<td>2003</td>
<td>52</td>
<td>52% male</td>
<td>80 ± 4.9</td>
<td>Cr EDTA clearance</td>
<td>49.2 ± 16.7</td>
<td>61 ± 23.8</td>
<td>All formulas demonstrated significantly different mean bias (p &lt; 0.001) but imprecision lowest for CG equation</td>
<td>CG gave an acceptable estimate of GFR</td>
</tr>
<tr>
<td>Burkhardt et al.</td>
<td>2005</td>
<td>61</td>
<td>52% male</td>
<td>74.6 ± 6.7</td>
<td>Inulin clearance</td>
<td>56.6 ± 17.7</td>
<td>76.5 ± 24.3</td>
<td>All estimations underestimated inulin clearance; lack of precision with all methods</td>
<td>MDRD disclosed the best quality but CG gives almost same results and easier to compute</td>
</tr>
<tr>
<td>Pequignot et al.</td>
<td>2009</td>
<td>121</td>
<td>46% male</td>
<td>86.1 ± 6.7</td>
<td>Creatinine clearance</td>
<td>40.9 (31-52.6)</td>
<td>61.3 (49.4-77)</td>
<td>MDRD had significantly greater bias compared to CG</td>
<td>CG significantly better than MDRD in elderly hospitalized pts</td>
</tr>
<tr>
<td>Roberts et al.</td>
<td>2009</td>
<td>68</td>
<td>50% male</td>
<td>65.1 ± 18.3</td>
<td>Gentamicin clearance</td>
<td>64.9 ± 28.2</td>
<td>89 ± 33</td>
<td>CG underestimated renal function (10%) while MDRD overestimated renal function (29%)</td>
<td>CG preferred method for hospitalized elderly pts</td>
</tr>
</tbody>
</table>

Case Study #1

- 90 yo female with CAD, HTN, and asthma admitted with LLE cellulitis.
- Wt=56 kg  Ht=62 in  SCr=0.85

\[
\begin{align*}
\text{CG-CrCl} &= 39 \text{ ml/min} \\
\text{MDRD} &= 63 \text{ ml/min/1.73m}^2 \\
\text{MDRD-CrCl} &= 57 \text{ ml/min}
\end{align*}
\]

- What dose of vancomycin should you start?
  A. 1 gm IV Q24H
  B. 1 gm IV Q12H
  C. 1 gm IV Q8H
Acute Delirium in the Elderly

What is the role of antipsychotics?

Case Study #2
- 85 yo male admitted s/p fall and found to have an UTI. Pt seems to be rambling to himself and unable to focus on what he is being told to do (a change from baseline per family). He is able to be re-directed with repeated instructions.
- What should you do next?
  A. No treatment is indicated at this time
  B. Start haloperidol 0.5 mg po Q4H prn agitation
  C. Start risperidone 1 mg po BID
  D. Start multi-component non-pharmacologic treatment strategies for delirium

Delirium in the Elderly
- An acute decline in attention and cognition
  - Present in 11-24% of elderly on hospital admission
  - Another 6-56% of pts will develop delirium during their hospital stay
- Associated with increased morbidity:
  - 1 year mortality rate of 35-40%
  - Increase hospital length of stay (21 vs. 9 days)
  - Higher risk of nursing home placement (33% vs. 11%)
  - Increase risk for dementia (63% vs. 8%)
  - Additional expenditure of $2500/patient
  - Accounts for $6.9 billion in annual Medicare expenditure (2004 data)

References:
Risk Factors For Delirium

- Sensory deprivation
- Medications (e.g., sedatives, hypnotics, narcotics, anticholinergic drugs, corticosteroids, polypharmacy, withdrawal or alcohol or other drugs)
- Acute neurological diseases (e.g., acute stroke (usually right parietal, hemorrhage, infarction, emorhage))
- Intensive illness (e.g., infections, acute organ failure, acute illness, sepsis, dehydration, poor nutritional status, trauma or trauma, viral infection)
- Metabolic derangement
- Surgery
- Environment (e.g., admission to an intensive care unit)
- Dementia or cognitive impairment
- Delirium risk factors
- History of delirium, stroke, neurological disease, falls or gait disorder
- Multiple comorbidities
- Male sex
- Chronic renal or hepatic disease

Management of Delirium

- Currently, no drug approved by FDA to treat delirium
- American Psychiatric Association recommendations (1999): low dose haloperidol as first-line agent in symptomatic management of delirium episodes

Efficacy of Antipsychotics for Delirium

- Findings from 2 meta-analyses and Cochrane Review:
  - No differences in efficacy and tolerability between conventional and atypical antipsychotics
  - Significant improvement in delirium scores
  - Reduced delirium severity by 43-70%
  - Remission by day 7 achieved in 69%
  - Improvement in delirium symptoms with lower doses of antipsychotics
Efficacy of Antipsychotics for Delirium

- Limitations of available studies:
  - Small sample sizes
  - Very few placebo controlled trials
  - Did not specify proportion of pts with hyperactive or hypoactive delirium
  - Short duration of observation
  - Few studies assessed medication safety

Adverse Events Associated with Antipsychotics

- FDA Public Health Advisories:
  - April 2005: Atypical antipsychotics associated with increased mortality (from CV events and infections) in elderly pts with dementia
  - June 2008: Both conventional and atypical antipsychotics associated with increased mortality in elderly pts treated for dementia-related psychosis

- Similar findings from many other retrospective studies on elderly taking antipsychotics (with or without dementia)
  - Higher rates for serious adverse events, cerebrovascular adverse events, mortality

Non-Pharmacologic Strategies for Delirium

- Multi-component protocols
  - Aim: to reduce underlying medical and environmental risk factors
  - Requires involvement of all healthcare discipline
  - Results from some prospective studies:
    - Decreased incidence of delirium by up to 50%
    - Reduced number of days of delirium
    - Reduced length of hospitalisation
    - Lowered mortality during hospital stay
Non-Pharmacologic Strategies for Delirium

Example Protocol:

<table>
<thead>
<tr>
<th>Targeted Intervention</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Use of clocks and calendars; remind patients of date, place, and reason for hospitalization</td>
</tr>
<tr>
<td>Sensory Perception</td>
<td>Remind patients to use their own glasses and hearing aids</td>
</tr>
<tr>
<td>Sleep Hygiene</td>
<td>Avoid treatments and vital signs during sleep period if possible; offer warm milk and tea before sleep</td>
</tr>
<tr>
<td>Mobilization</td>
<td>Get pts out of bed daily; avoid continuous IV fluids; remove urinary catheter if possible; avoid physical restraints</td>
</tr>
<tr>
<td>Hydration and Nutrition</td>
<td>Encourage oral fluid intake daily; add nutritional supplement if indicated</td>
</tr>
<tr>
<td>Review Medication List</td>
<td>Avoid psychoactive and sedative drugs if possible; discontinuation medications with anticholinergic side effects</td>
</tr>
</tbody>
</table>

Bottom Line

Role for antipsychotics:

- Should be reserved only for patients with symptoms that threaten the safety of themselves or others
- Additional Considerations:
  - Discussion with family regarding potential risks
  - Obtain ECG prior to initiation and periodic ECG monitoring
  - Start with low doses and titrated slowly to lowest effective dose
  - Evaluate need for therapy continuation frequently

Case Study #2

85 yo male admitted s/p fall and found to have an UTI. Pt seems to be rambling to himself and unable to focus on what he is being told to do (a change from baseline per family). He is able to be re-directed with repeated instructions.

What should you do next?

A. No treatment is indicated at this time
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C. Start risperidone 1 mg po BID
D. Start multi-component non-pharmacologic treatment strategies for delirium
Hip Fractures and the Elderly

When should bisphosphonates be initiated and should vitamin D be repleted first?

Case Study #3

- 75 yo female admitted with a right femoral neck fracture after a mechanical fall at home. The pt was taken to the OR the next day and had a right hip replacement.
  - Labs: SCr=0.9  25(OH)D=22 ng/mL
- When should a bisphosphonate be initiated?
  A. No bisphosphonate is indicated
  B. After complete recovery from hip replacement surgery
  C. As soon as vitamin D is replete
  D. On discharge from the hospital

Hip Fractures

- One of the most common type of osteoporotic fracture
- Incidence increases exponentially after the age of 70
- Associated with:
  - 2.5 fold increase in risk for future fractures
  - 10-20% excess mortality within one year
  - Loss of functional independence in majority of survivors
  - Only 40% regain their previous level of independence
  - Nearly 75% of fracture related healthcare expenditures in the elderly
- Anticipated to more than double by 2025 and quadruple by 2050 secondary to increases in both the numbers of elderly and incidence of fracture at a given age
Bisphosphonates and Fracture Healing

**Benefits:**
- Prevent disuse osteopenia
- Reduce risk of future fractures by about 50%

**Risks:**
- May delay fracture healing by interfering with hard callus remodeling process

Findings from Small Controlled Studies

- **Adolphson et al. 2000**
  - 32 female pts (mean age 62) with distal radius fracture randomized to clodronate vs. placebo for 8 wks
  - Results:
    - Increase in BMD of fracture region (53% vs. 33%; p=0.01)
    - No difference in fracture position between the groups

- **Van Del Poest Clement et al. 2002**
  - 44 pts (44% female; mean age 46) with tibial fracture randomized to alendronate vs. placebo for 1 yr
  - Results:
    - Prevented bone loss from hip of fractured side (2.1% vs. -4.5%; p=0.04)
    - No difference in incidence of mal-union (1 in each group)
Findings from Observational Studies

- **Solomon et al. 2009** –
  - Nested case-control study of 81 cases and 810 controls (80% female; mean age 77) with humerus fractures
  - **Results:**
    - Incidence of non-union procedure = 0.41%
    - Bisphosphonate use associated with increased odds of non-union (OR 2.37; 95% CI 1.13-4.96)

- **Rozental et al. 2009** –
  - Retrospective study of 196 pts (79% female; mean age 68) with distal radius fractures
  - Group divided based on use of bisphosphonate for at least 1 month (BP group = 43 pts; control group = 153 pts)
  - **Results:**
    - Fracture union occurred in all pts in both groups
    - Bisphosphonate use associated with a slightly longer time to radiographic union (58±17 vs. 49±14 days; p=0.01)

HORIZON Recurrent Fracture Trial

- **Lyles et al. 2007** –
  - Randomized trial of 2127 with recent hip fracture
    - Yearly IV zoledronic acid vs. placebo
    - Mean age: 74±9 years
    - Mean follow-up period: 1.9 years
    - 41.8% with baseline T score < -2.5 SD at the femoral neck
  - **Results:**
    - Decreased new clinical fractures (8.6% vs. 13.9%, p=0.001)
    - Increased BMD at femoral neck (3.6% vs. -0.7% at 36 mos; p < 0.001)
    - No difference in incidence of delayed fracture union (3.2% vs. 2.7%; p=0.61)

Bisphosphonates and Vitamin D Deficiency

- **Vitamin D deficiency**
  - Defined as 25(OH)D < 30 ng/mL
- **Findings from studies on patients receiving bisphosphonates:**
  - Higher BMD in vitamin D replete vs. deficient pts
  - BMD increased with vitamin D use in pts previously considered non-responsive to bisphosphonates
  - Failure to normalize vitamin D level associated with
    - Further BMD loss
    - Higher incidence of fractures
Case Study #3

- 75 yo female admitted with a right femoral neck fracture after a mechanical fall. Patient underwent a right hip replacement the next day.
  - Labs: SCr=0.9  25(OH)D= 22 ng/mL
- When should a bisphosphonate be initiated?
  A. No bisphosphonate is indicated
  B. After complete recovery from hip replacement surgery
  C. As soon as vitamin D is replete
  D. On discharge from the hospital

CONCLUSIONS

- GFR estimation equations for drug dosing:
  - MDRD tends to overestimate GFR in the elderly
  - Use CG equation for drug dosing until new method available
- Acute delirium in the elderly:
  - Modifying or eliminating risk factors is key for management
  - Antipsychotics should be reserved for severe agitation only
- Use of bisphosphonates after hip fracture:
  - Currently, benefits of preventing future fractures outweigh potential risk of delayed healing
  - Bisphosphonates should be initiated when 25(OH)D level is ≥ 30 ng/mL