Journal Club

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1395.8.16
Appropriate Antibiotic Use in Adults with Acute Respiratory Tract Infections

Harris AM et al. *Ann Intern Med* 2016 Jan 19
Antibiotics?
Antibiotics should not be prescribed for most patients with uncomplicated bronchitis, sore throat, or acute rhinosinusitis.

Sponsoring Organizations: American College of Physicians (ACP), Centers for Disease Control and Prevention (CDC)

Target Audience: All clinicians who provide care to adults in ambulatory settings
Antibiotics are prescribed during more than 100 million adult ambulatory visits annually; an estimated 50% of these prescriptions might be unnecessary or inappropriate.

This paper from the ACP and the CDC is an update of 2001 guidelines on appropriate antibiotic use for acute respiratory tract infection in adults and includes advice on managing bronchitis, pharyngitis, and rhinosinusitis. The focus of the update is healthy adults without chronic lung disease or immunocompromising conditions.
Acute uncomplicated bronchitis

- More than 90% is **viral**; cough can last as long as **6 weeks** and might be associated with mild constitutional symptoms.

- Purulent sputum or a change in its color does **not signify bacterial infection**; purulence results from the presence of inflammatory cells or sloughed mucosal cells.
 Patients might benefit from symptomatic relief (e.g., cough suppressants, expectorant)

- It should be differentiated from pneumonia, which is unlikely in the absence of tachycardia, tachypnea, fever >38°C, and abnormal chest exam

**Clinicians should not perform testing or initiate antibiotics unless pneumonia is suspected**
Pharyngitis

- Pharyngitis most often is viral; a viral etiology is more likely in patients with associated cough, nasal congestion, conjunctivitis, or oral ulcers or vesicles.
Patients with fewer than three Centor criteria (i.e., fever by history, tonsillar exudates, tender anterior cervical adenopathy, absence of cough) have a low probability of group A streptococcal infection and do not require further testing.
Oral antibiotics (e.g., penicillin, amoxicillin) should be prescribed **only** if group A streptococcal pharyngitis is confirmed.
Acute rhinosinusitis (duration range, 1–33 days) usually is caused by a viral infection associated with the common cold; symptom include nasal congestion, purulent nasal discharge, maxillary tooth pain, facial pain, fever, and ear pain.
Acute bacterial rhinosinusitis can develop secondary to a viral upper respiratory infection (URI); however, fewer than 2% of viral URIs are complicated by bacterial rhinosinusitis.

Given the similar radiographic appearance of viral sinusitis and bacterial sinusitis, imaging is not helpful.
Antibiotics should be reserved for patients whose symptoms persist for >10 days, are severe (i.e., fever >39°C, purulent nasal discharge, facial pain for >3 consecutive days), or deteriorate after initial improvement.

The 2012 Infectious Diseases of America guidelines recommend amoxicillin-clavulanate as the preferred agent if antibiotics are deemed to be necessary.
In patients with hypertension, beta-blockers in the 120 d before noncardiac surgery were linked to CV events and death.

Question

In patients with hypertension who are having noncardiac surgery, is long-term beta-blocker treatment associated with major adverse cardiovascular (CV) events (MACE) or mortality during the perioperative period?
**Methods**

- **Patients:**
  55,320 adults ≥ 20 years of age (mean age 66 y, 59%* women) who had hypertension (based on the use of ≥ 2 of β-blockers, renin–angiotensin system [RAS] inhibitors, calcium antagonists, or thiazides) and had noncardiac surgeries.

- **Exclusion criteria:**
  included liver disease, renal disease, secondary CV conditions, use of sotalol hydrochloride, or treatment with all 4 classes of study drugs.
 **Design:**
Cohort study with linkage of national databases.

 **Setting:** Denmark.

 **Risk factors:**
Filled prescriptions for -blockers, RAS inhibitors calcium antagonists, or thiazides in the 120 day before before surgery.

 **Outcomes:**
MACE (CV death, nonfatal ischemic stroke, or non fatal myocardial infarction) and mortality within 30 days after surgery.
Main results

Compared with RAS inhibitors plus thiazides, combinations of b-blockers plus RAS inhibitors, calcium antagonists, or thiazides were associated with MACE and mortality.
Association between perioperative antihypertensive treatment and cardiovascular events and death in patients with hypertension who are having noncardiac surgery†

<table>
<thead>
<tr>
<th>Antihypertensive treatments</th>
<th>Adjusted odds ratio (95% CI) at 30 d after surgery‡</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MACE</td>
</tr>
<tr>
<td>β-blocker + RAS inhibitor</td>
<td>2.16 (1.54 to 3.04)</td>
</tr>
<tr>
<td>β-blocker + calcium antagonist</td>
<td>2.17 (1.48 to 3.17)</td>
</tr>
<tr>
<td>β-blocker + thiazide</td>
<td>1.56 (1.10 to 2.22)</td>
</tr>
<tr>
<td>β-blocker + 2 others</td>
<td>1.22 (0.90 to 1.64)</td>
</tr>
<tr>
<td>RAS inhibitor + calcium antagonist</td>
<td>1.12 (0.82 to 1.54)</td>
</tr>
<tr>
<td>RAS inhibitor + thiazide + calcium antagonist</td>
<td>0.97 (0.73 to 1.29)</td>
</tr>
<tr>
<td>Calcium antagonist + thiazide</td>
<td>1.02 (0.73 to 1.44)</td>
</tr>
</tbody>
</table>

†MACE = major adverse cardiovascular events; RAS = renin-angiotensin system; CI defined in Glossary.

‡Compared with RAS inhibitors + thiazides. Adjusted for sex, age, body mass index, year, comorbidities, pharmacotherapies, and surgery risk.
Conclusion

In patients with hypertension, b-blocker treatment in combination with other antihypertensive drugs in the 120 days before noncardiac surgery was associated with increased risk for major adverse cardiovascular events and mortality compared with combinations that did not include a b-blocker.
Commentary

- Perioperative treatment with -blockers in noncardiac surgery remains controversial.

- 2 recent systematic reviews showed that perioperative initiation of b-blockers was associated with both increases in all-cause mortality and cerebrovascular events, probably related to increased hypotension and bradycardia and reductions in acute myocardial infarction and supraventricular tachycardia.
Variability of results within study cohorts was, in part, attributable to differences in surgical risk, type and dose of b-blockade, and duration of b-blocker exposure before surgery.

Perioperative management of patients on long term b-blockers was not addressed, although current guidelines recommend continuing b-blockers
The registry-based cohort study by Jorgensen and colleagues found that long-term use of \( b \)-blockers plus other antihypertensive agents was associated with \textit{increased risk} for MACE and all-cause mortality compared with combination therapy without \( b \)-blockade.

The findings are subject to the potential biases that threaten the validity of all observational studies.
- b-blockers are no longer considered first-line agents for hypertension;

- some guidelines do not even recommend them as second- or third-line agents because they are usually less effective than other treatments at reducing risk for CV events
The study by Jorgensen and colleagues identifies another area of uncertainty in the use of -blockers during the perioperative period.

The existing literature is not sufficient to change practice.

A clinical trial is needed to address the perioperative management of patients receiving long-term -blockers.
In high-risk ulcers, intermittent and continuous PPI therapy do not differ for recurrent bleeding.

Question

In patients with high-risk bleeding ulcers, what is the efficacy of intermittent proton-pump inhibitor (PPI) therapy compared with bolus plus continuous infusion PPI therapy?
Review scope

- Included studies compared intermittent boluses of PPIs (any dose, frequency, or route) with IV PPI bolus (80 mg) followed by continuous infusion (8 mg/h for 72 h) in patients with upper gastrointestinal bleeding who were found to have a gastric or duodenal ulcer with active bleeding, a nonbleeding visible vessel, or an adherent clot; and had successful endoscopic hemostatic therapy.

- Ulcers with flat spots and clean bases were excluded.

- Primary outcome was recurrent bleeding within 7 days. Other outcomes included recurrent bleeding at 3 days and 30 days, and mortality.
Review methods

MEDLINE, EMBASE/Excerpta Medica, and Cochrane Central Register of Controlled Trials (all to Dec 2013), reference lists, and major gastroenterology conference proceedings (2009 to 2013) were searched for randomized controlled trials.

13 RCTs (n = 1733) met selection criteria. 8 RCTs had Adequate randomization; 1 had adequate allocation concealment; 5 had blinding of patients, personnel, and outcome assessors; and 12 had adequate follow-up.
Main results

- Intermittent PPIs were noninferior to bolus plus continuous PPIs for recurrent bleeding at 7 days, 3 days, and 30 days and mortality.

- Groups did not differ for recurrent bleeding using standard analyses.
Intermittent proton-pump inhibitors (PPIs) vs bolus plus continuous-infusion PPIs in patients with high-risk bleeding ulcers*

<table>
<thead>
<tr>
<th>Recurrent bleeding</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRR (95% CI)</th>
<th>ARD (upper 95% CI)†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Intermittent PPI</strong></td>
<td><strong>Bolus + continuous PPI</strong></td>
<td></td>
</tr>
<tr>
<td>At 7 d</td>
<td>10 (1373)</td>
<td>6.9%</td>
<td>9.4%</td>
<td>26% (−6 to 48)</td>
</tr>
<tr>
<td>At 3 d</td>
<td>9 (1173)</td>
<td>8.1%</td>
<td>11%</td>
<td>23% (−10 to 46)</td>
</tr>
<tr>
<td>At 30 d</td>
<td>13 (1733)</td>
<td>7.9%</td>
<td>8.7%</td>
<td>9% (−24 to 33)</td>
</tr>
</tbody>
</table>

*ARD = absolute risk difference; other abbreviations defined in Glossary. Weighted event rates, RRR, and CI calculated from control event rates and risk ratios for the intention-to-treat population in article using a fixed-effect model.

†Intermittent PPIs were noninferior (upper boundary of the 95% CI for the ARD was < 3% at each time point). Analysis was per protocol.
Conclusion

In patients with high-risk bleeding ulcers, intermittent proton pump inhibitor (PPI) therapy does not differ from bolus plus continuous-infusion PPI therapy for recurrent bleeding.
Commentary

Hemodynamically stable patients without serious comorbid conditions who have low-risk ulcers (e.g., clean-based, flat, pigmented spots) on endoscopy can be discharged on once-daily oral PPIs.
In contrast, patients with bleeding from upper gastrointestinal tract ulceration and evidence of high-risk stigmata after successful endoscopic hemostasis benefit from high-dose parenteral PPI therapy (i.e., bolus followed by continuous infusion PPIs for 72 h)
Meta-analyses of RCTs of high-dose PPI therapy have shown reductions in further bleeding, surgery, and mortality compared with endoscopic therapy alone.
The recommendation for high-dose continuous infusion PPIs is based on the hypothesis that maintaining intragastric pH > 6 maximizes clot stabilization and prevents recurrent ulcer bleeding.
The unresolved question is whether intermittent PPIs are an acceptable alternative to continuous-infusion PPIs.

RCTs comparing intermittent and bolus plus continuous-infusion PPI therapy have been limited by small sample sizes, and prior meta-analyses have been inconclusive due to methodologic issues of including patients without high-risk stigmata or who did not have endoscopic therapy, and comparisons of high-vs-low-dose PPIs rather than continuous vs intermittent infusion.
The review found that intermittent PPI therapy was noninferior to bolus plus continuous-infusion PPI therapy for recurrent bleeding within 7 days, 3 days, and 30 days; need for surgery or urgent interventions, blood transfusions, length of stay; and mortality.
Although overall recurrent bleeding rates were low in all studies, the meta-analysis supports the use of **intermittent PPI therapy** for high-risk ulcer bleeding as an alternative to bolus plus continuous infusion PPI dosing, which is more costly and resource-intensive.

It's time for future guidelines to reflect this treatment option.
Image in clinical medicine
Neurogenic Megacolon in Spinal Cord Injury

Patient with Large, Intermittent Waves of Peristalsis.
A 44-YEAR-OLD MAN WITH A 20-YEAR HISTORY OF QUADRIPLEGIA FROM A gunshot wound to the neck presented to the emergency department with symptoms of a urinary tract infection. His medical history included chronic megacolon and neurogenic bladder, and he had been admitted to the hospital many times for the management of urinary tract infections and constipation. On physical examination, his abdomen was distended, soft, nontender, and tympanic to percussion, with normal bowel sounds. Extremely large, intermittent waves of peristalsis were noted (see video), and the patient reported mild cramping and a bloating sensation in association with this finding. Computed tomography of the abdomen revealed massive dilatation of the transverse (Panels A and B), descending, and sigmoid colon of up to 18 cm. There was also a substantial fecal burden as a result of neurogenic dysfunction (Panels A and B, asterisks). Stool softeners and laxatives were administered, and the patient was told to avoid antimitotility agents. Megacolon is prevalent in patients with spinal cord injuries, especially in older patients and in those with injuries that have been present for more than 10 years. Complications of megacolon include abdominal compartment syndrome, volvulus, and fecal impaction. Definitive treatment includes colectomy, colostomy, or both. This patient opted for conservative medical management of his neurogenic megacolon in accordance with his symptoms.
THANKS FOR YOUR ATTENTION