An Expected Systemic Reaction with Unexpected Costs to the System

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Introduction

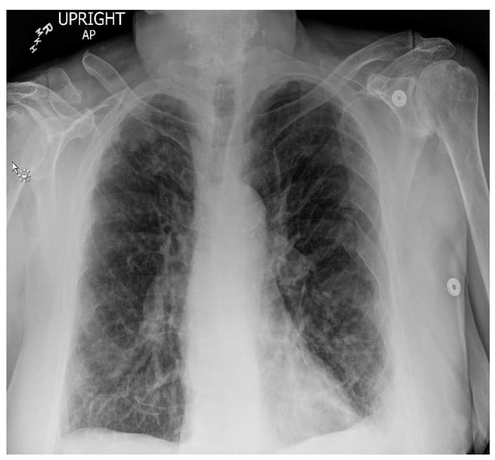
- Zoledronic acid is a commonly administered IV bisphosphonate for fracture prevention in osteoporosis. The evidence base for its effectiveness and cost-effectiveness is strong in post-menopausal women, but its effectiveness in men is largely based on extrapolation and surrogate markers.
- The Acute Phase Response (APR) is a common adverse event of ZA administration that affects 40-60% of patients and involves fevers, arthralgias, myalgias and weakness.

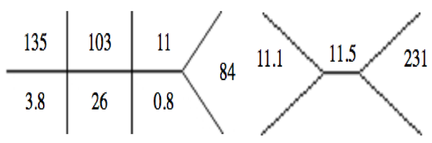
Case presentation

A 67-year-old man with COPD and schizophrenia presented for outpatient management of osteoporosis. Because of poor dentition and dysphagia, he received 5mg intravenous zolendronic acid, which he tolerated without symptoms or premedication.

He presented to the ER the following day with chills, myalgias, diffuse weakness and an inability to walk or care for himself at his adult foster home. On interview, he denied symptoms of infection or concerning exposures.

On exam, vitals were notable for Tmax 39.3 C, HR 100bpm, and BP 147/85. He was ill-appearing with diffuse pain with limb movement and 3/5 strength in upper and lower extremities without sensation, cranial nerve or cerebellar abnormalities; other exam components were benign and without stigmata of infection.





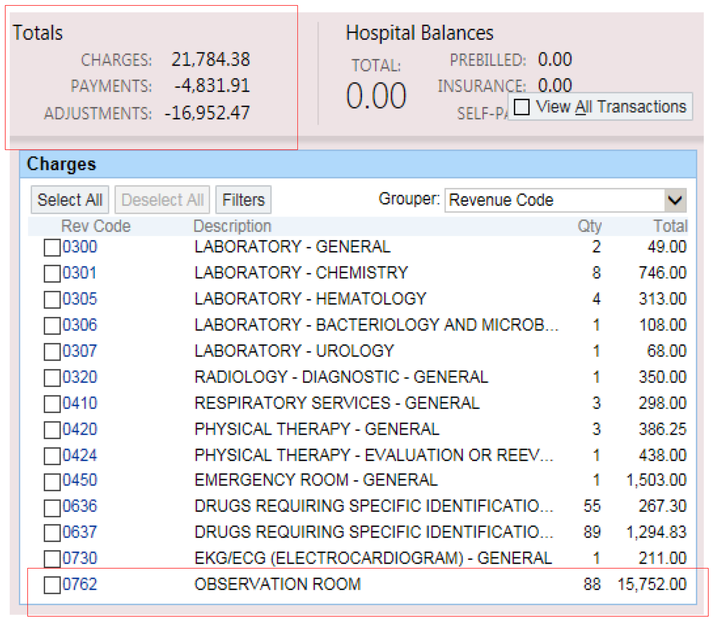
Ca++: 8.1	T.Bili: 0.4
Lactate: 0.8	Alb: 3.2
Trop: <0.02	INR: 1.0
AST: 18	CK: 174
ALT: 27	ESR: 29
Alk Phos: 59	CRP: 49

Blood cultures from admission:
- no growth after 5 days

Clinical Course

The possibility of a zolendronic acid-induced acute phase reaction was promptly raised, and additional imaging and empiric antibiotics were not pursued. He was admitted on Observation Status. Blood and urine cultures originally obtained remained negative.

His hospital course was notable for ongoing diffuse myalgias and weakness and by HD3 was still only able to stand with assistance and unable to walk 10 feet with his walker, far from his baseline of twenty blocks. SNF placement was delayed because of insurance barriers caused by his Observation Status. He ultimately required a 3 week SNF stay before returning to his prior living arrangement.


Totals
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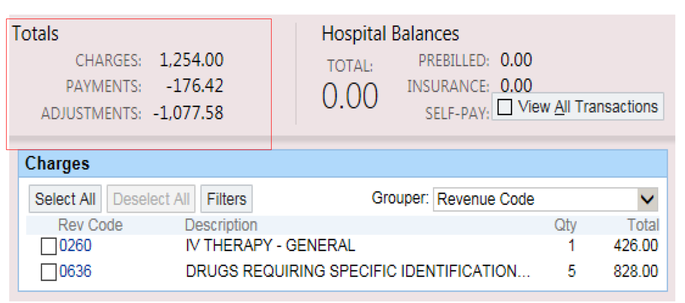
PAYMENTS: -4,831.91
ADJUSTMENTS: -16,952.47

Hospital Balances
TOTAL: 0.00
PREBILLED: 0.00
INSURANCE: 0.00
SELF-PAY:
View All Transactions

Charges

Select All | Deselect All | Filters | Grouper: Revenue Code

Rev Code	Description	Qty	Total
0300	LABORATORY - GENERAL	2	49.00
0301	LABORATORY - CHEMISTRY	8	746.00
0305	LABORATORY - HEMATOLOGY	4	313.00
0306	LABORATORY - BACTERIOLOGY AND MICROB...	1	108.00
0307	LABORATORY - UROLOGY	1	68.00
0320	RADIOLOGY - DIAGNOSTIC - GENERAL	1	350.00
0410	RESPIRATORY SERVICES - GENERAL	3	298.00
0420	PHYSICAL THERAPY - GENERAL	3	386.25
0424	PHYSICAL THERAPY - EVALUATION OR REEV...	1	438.00
0450	EMERGENCY ROOM - GENERAL	1	1,503.00
0636	DRUGS REQUIRING SPECIFIC IDENTIFICATIO...	55	267.30
0637	DRUGS REQUIRING SPECIFIC IDENTIFICATIO...	89	1,294.83
0730	EKG/ECG (ELECTROCARDIOGRAM) - GENERAL	1	211.00
0762	OBSERVATION ROOM	88	15,752.00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PAYMENTS: -176.42
ADJUSTMENTS: -1,077.58

Hospital Balances
TOTAL: 0.00
PREBILLED: 0.00
INSURANCE: 0.00
SELF-PAY:
View All Transactions

Charges

Select All | Deselect All | Filters | Grouper: Revenue Code

Rev Code	Description	Qty	Total
0260	IV THERAPY - GENERAL	1	426.00
0636	DRUGS REQUIRING SPECIFIC IDENTIFICATION...	5	828.00

Outcome	Number needed to treat/Harm
Radiographic fracture prevention	33[1]
Clinical fracture prevention	Unknown
APR-related AEs	2-3
APR-related serious AEs	Unknown

Discussion

The APR is a well-described and common complication of Zoledronic acid administration, and affects 40-60 % of patients in some form. However, the frequency with which it causes APRs of this severity—and thus the total burden to patients and the health care system—remains unknown. A recent review of the APR demonstrated the frequency of individual components of the APR (e.g. fevers, myalgias), but no estimate of the outcomes these symptoms ultimately caused.[2]

This is likely because this data does not exist: large clinical trials of ZA only report the frequencies of APR components, with no estimate of the frequency and associated costs of hospitalizations in cases like this one. It is unclear whether this is because cases like this are truly so rare as to go uncaptured, or rather because we take "self-limited", symptomatic complications like these too lightly to bother studying them in detail. Ideally we would not be causing hospitalizations for therapies that offer improvements in mere surrogate outcomes.

This was a therapeutic intervention with marginal evidence for a true clinical benefit (see table above), for which the patient suffered a substantial complication. Further study and a more granular analysis of the range of severities and consequences from ZA-associated APR would provide clarity on the true costs and benefits of ZA and identify patients at risk for hospitalization or functional decline requiring SNF placement. This appears particularly important in the subgroup that our patient represents: frail older patients with marginal self-care capability who are at high risk both for receiving ZA and suffering its consequences.

References:

1. Boonen, Steven *et al.* Fracture Risk and Zoledronic Acid Therapy in Men with Osteoporosis. In: *New England Journal of Medicine*, 2012, vol. 367, n° 18, p. 1714-1723.
2. Reid, I. R., et al. "Characterization of and risk factors for the acute-phase response aftef zoledronic acid." *The Journal of Clinical Endocrinology & Metabolism* 95.9 (2010).