THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"A 73 year old man presents with hypoglycemia"

Dr. Dickens does not have any relevant financial relationships with any commercial interests.

ENDORAMA

Laura Dickens

January 26, 2017

Objectives

1. Review the causes and evaluation of hypoglycemia in patients without diabetes
2. Review the differential diagnosis for hyperinsulinemic hyperglycemia
3. Understand alterations in the response to insulin-induced hypoglycemia in patients with spinal cord injuries

Chief complaint

73 year old man with a PMH of functional quadriplegia 2/2 remote traumatic C-spine injury, chronic Ogilvie syndrome, and neurogenic bladder with chronic indwelling foley presents with AMS and hypoglycemia.

HPI

- The patient's family noticed slurred speech and confusion. EMS was called and **blood sugar found to be 47**. He received 1-2 amps of D50 and mental status returned to baseline.
- **No history of diabetes.**
- Pt denies any other symptoms new from his baseline. He denied fevers, chills, HA, blurred vision, chest pain, abdominal pain, SOB, N/V. He endorsed normal PO intake.

HPI, continued

- Of note, he has a known history of **chronic Ogilvie syndrome** and has marked abdominal distention at baseline. Last BM was yesterday; bowel regimen includes Ducolax suppositories every other day.
- Also of note, he was admitted three weeks ago for sepsis and was ultimately found to have prostatitis on CT for which he was discharged on a regimen of Ciprofloxacin and Bactrim (per ID) for a 12 week course.

Additional History

ROS: +abdominal distention +muscle spasms, otherwise negative

Past Medical History:

- C spine injury from GSW in 1986, functional quadriplegia
- Chronic Ogilvie syndrome
- Neurogenic bladder with chronic indwelling foley
- Osteoporosis (reported, no BMD in our system)
- Hyperlipidemia

Past Surgical History: None

Family History: Hypertension (mother)

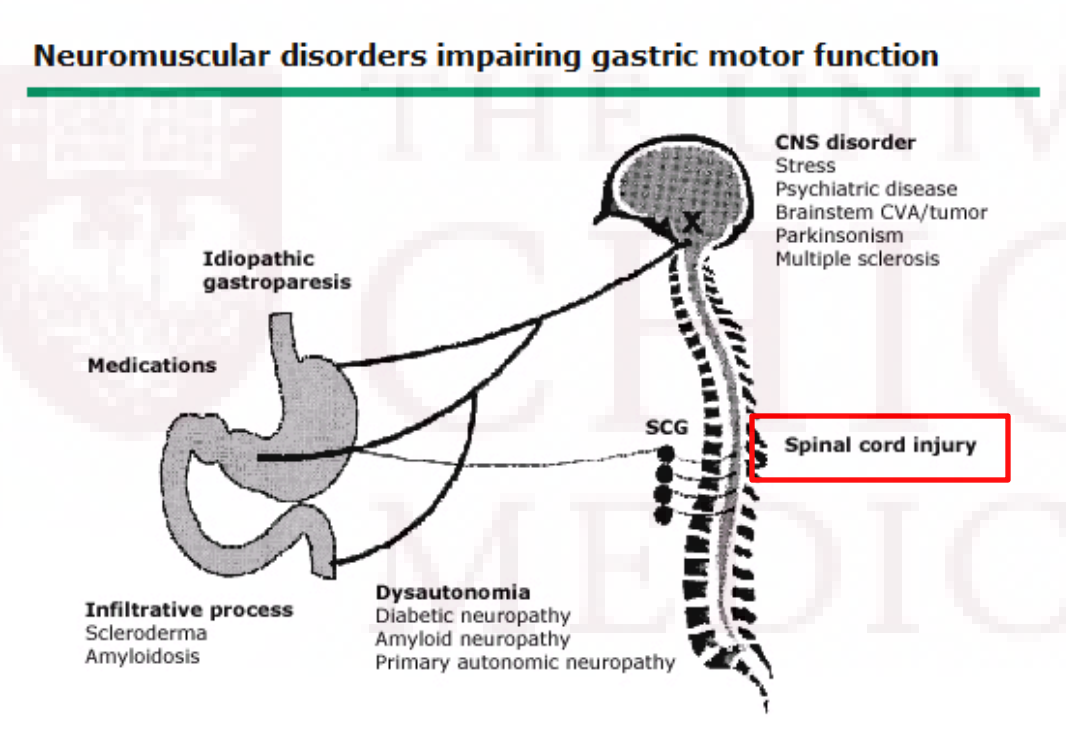
Additional History

Meds:

- Aspirin 81mg daily
- Calcium carbonate 500mg and Vitamin D3 2,000IU daily
- Dantrolene 50mg TID
- Ezetimibe 10mg daily
- K-dur 10 mEq daily
- Bactrim DS 2 tabs TID
- Ciprofloxacin 750mg BID

Social Hx: Former smoker (quit 40+ years ago), occasional ETOH, no drugs. Lives with wife, has a homemaker and home nurse. Dependent on caretakers for all ADLs and iADLS.

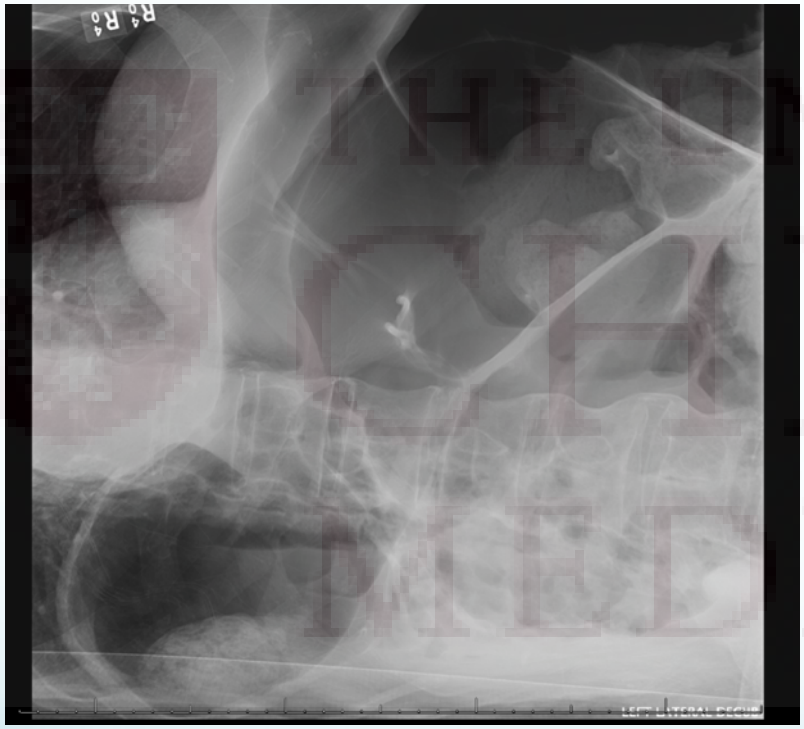
Ogilvie syndrome? Chronic Intestinal Pseudo-Obstruction

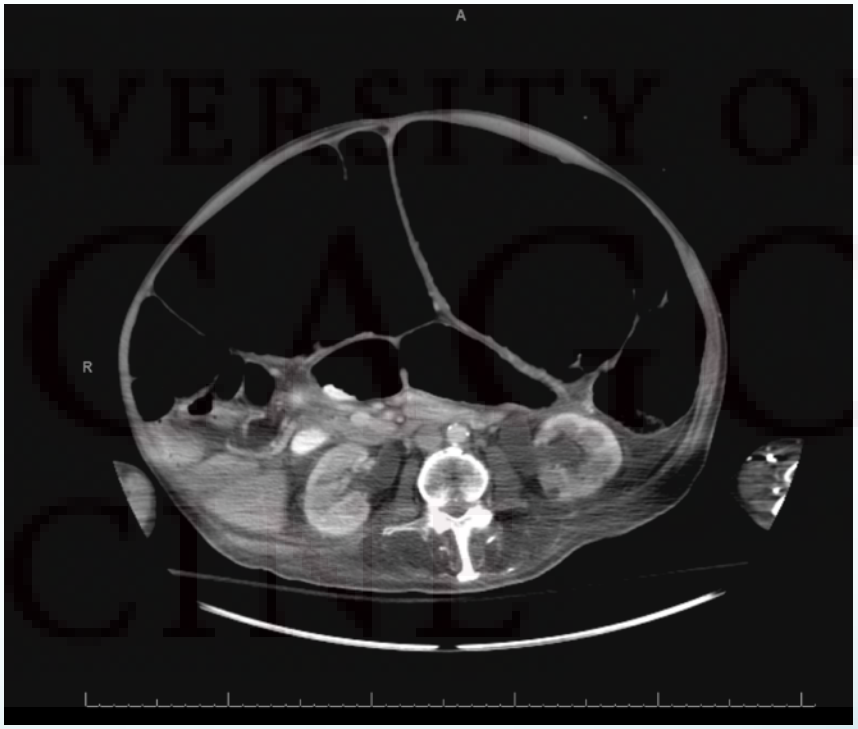


- Signs/symptoms of mechanical obstruction with no anatomic lesion
- Dilated bowel on imaging
- Causes include degenerative neuropathies, paraneoplastic, infectious, autoimmune

Up To Date. Chronic intestinal pseudo-obstruction.

Our Patient's Imaging





Marked colonic distention

Physical exam

VITALS: Temp 36, BP 119/49, HR 72, RR 18, O2 sat 100% on RA, **BMI 17**

Constitutional: He is oriented to person, place, and time.
Thin black man in no distress, notable supraclavicular wasting

HENT: Normocephalic and atraumatic. Oropharynx is clear and moist. White patches on the lateral tongue

Eyes: Conjunctivae are normal. No scleral icterus.

Neck: Neck supple. No thyromegaly present.

Cardiovascular: Normal rate, regular rhythm and normal heart sounds.

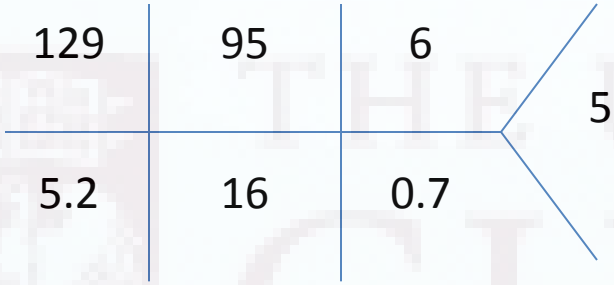
Pulmonary/Chest: Effort normal and breath sounds normal. He has no wheezes.

Abdominal: He exhibits distension. There is no rebound and no guarding.
Markedly distended abdomen, non-tender

Musculoskeletal: **Muscular atrophy of the bilateral lower extremities, 0/5 strength in the LE. Bilateral UE with shoulder shrug intact**

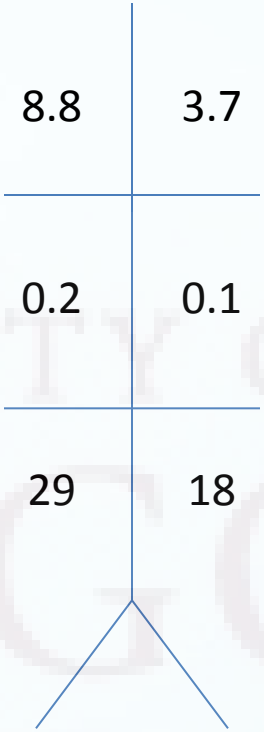
Neurological: He is alert and oriented to person, place, and time.

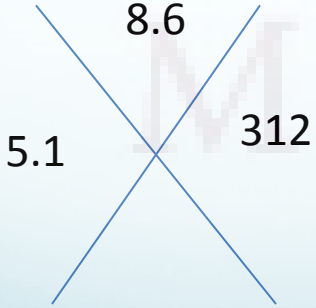
Admission Labs



Cr baseline 0.4-0.5

Ca 9.1
Mg 1.7
Ph 2.6





Hgb baseline 8-9

A1c 4.3
TSH 1.70

Blood and urine cultures- pending
UA: +LE, negative nitrites, occasional bacteria and squamous cells, many yeast

Chart review

	Glucose, Ser/Plasma
Ref. Range	Latest Ref Range: 60 - 99 mg/dL
11/1/2004 0237	43 ↓
11/1/2004 0526	89
11/1/2004 1402	134 ↑
11/2/2004 0148	102
11/2/2004 0628	102
11/2/2004 1357	137 ↑
11/3/2004 0420	91
11/4/2004 0600	79
11/4/2004 2200	89
11/5/2004 2203	93
11/6/2004 2213	97
10/13/2014 1150	76
10/14/2014 0630	71
10/15/2014 0448	96
4/7/2015 1359	100
4/7/2015 1744	98
12/31/2015 1320	112 ↑
12/31/2015 2225	101
1/1/2016 0557	92
11/4/2016 2051	105 * ↑
11/5/2016 2031	52 * ↓
11/6/2016 0637	40 * ↓
11/7/2016 0825	107 * ↑
11/7/2016 1651	129 * ↑
11/8/2016 0417	111 * ↑
11/8/2016 1715	79 *
11/9/2016 0651	87 *
11/9/2016 1701	87 *

- 11/2004 – admitted with pyelonephritis and bacteremia
- 11/5/16 – admitted with sepsis from prostatitis

Differential diagnosis?
Initial recommendations?

Initial Management

- Admitted to general medicine
- Started on IV ceftriaxone and Bactrim for possible UTI. Cipro held due to reports of causing hypoglycemia.
- Started on D5 NS @ 100 cc/hr
- On the floor had 4 episodes of hypoglycemia requiring 2 amps of dextrose. Lowest POC 34.
- Transferred to MICU for more intensive monitoring

Causes of Hypoglycemia

TABLE 1. Causes of hypoglycemia in adults

Ill or medicated individual
1. Drugs
   - Insulin or insulin secretagogue
   - Alcohol
   - Others (Table 2)
2. Critical illnesses
   - Hepatic, renal, or cardiac failure
   - Sepsis (including malaria)
   - Inanition
3. Hormone deficiency
   - Cortisol
   - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
4. Nonislet cell tumor

Seemingly well individual
5. Endogenous hyperinsulinism
   - Insulinoma
   - Functional β-cell disorders (nesidioblastosis)
     - Noninsulinoma pancreatogenous hypoglycemia
     - Post gastric bypass hypoglycemia
   - Insulin autoimmune hypoglycemia
     - Antibody to insulin
     - Antibody to insulin receptor
   - Insulin secretagogue
   - Other
6. Accidental, surreptitious, or malicious hypoglycemia

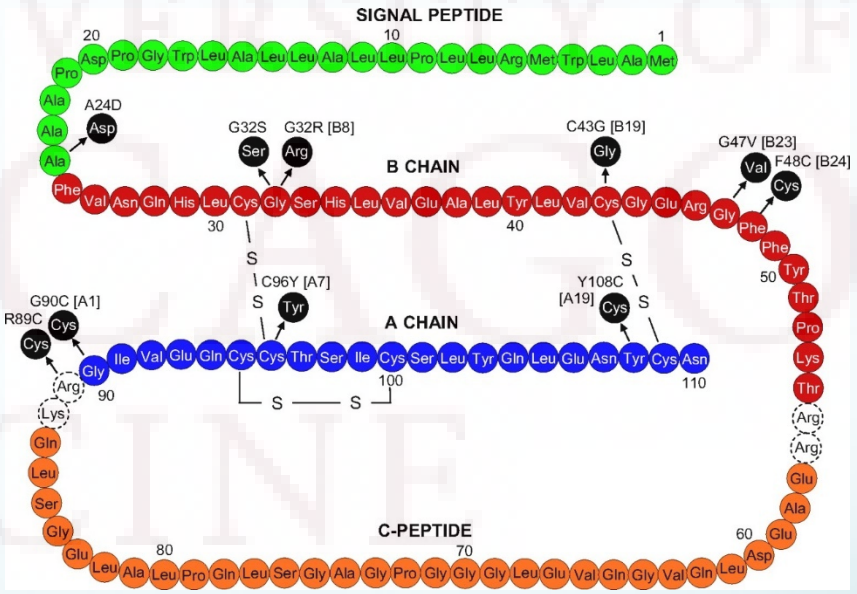


Table: Cryer et al. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.
Image: Støy et al. Proc Natl Acad Sci U S A. 2007 Sep 18;104(38):15040-4.

Quadraplegia and response to hypoglycemia

- 10 parapleglic, 10 quadriplegic, 10 controls
- Injected with IV regular insulin: 0.1 unit/kg for paraplegic and control, 0.2 unit/kg for quadriplegic)
- Serial measurements of glucose, epinephrine, norepinephrine, dopamine, cortisol obtained

TABLE 2

EFFECT OF INSULIN ON PLASMA GLUCOSE LEVELS (mg/100 ml)

Subjects (Number)	Time After Insulin Administration (min) 0	30	45	60	75	90
Control (8)	95 ± 2.8	35 ± 2.5*	52 ± 4.9*	63 ± 7.4*	66 ± 6.0*	72 ± 4.1*
Paraplegic (7)	90 ± 2.6	37 ± 4.0*	52 ± 4.0*	60 ± 8.4*	78 ± 2.3	70 ± 3.0
Quadriplegic (8)	91 ± 1.0	60 ± 4.8*†	60 ± 3.0*	67 ± 5.2*	79 ± 5.7	83 ± 8.5

*$p<0.01$ between 0 and 30, 45, 60, 75, 90 minutes.
†$p<0.01$ between control and paraplegic or quadriplegic subjects.

Naftchi et al. Peptides. 1985;6 Suppl 1:85-94.

TABLE 4

EFFECT OF INSULIN-INDUCED HYPOGLYCEMIA ON PLASMA EPINEPHRINE LEVELS (pg/ml)

Subjects (Number)	Time After Insulin Administration (min)						
	−5	0	30	45	60	75	90
Control (8)	87 ± 32	71 ± 14	480 ± 155*	963 ± 163*	561 ± 135*	297 ± 52*	239 ± 36*
Paraplegic (7)	93 ± 13	81 ± 12	187 ± 91*	369 ± 170*	165 ± 33*	123 ± 15*	124 ± 17*
Quadriplegic (8)	54 ± 11	51 ± 11	57 ± 12†	62 ± 12†	65 ± 13†	67 ± 18†	71 ± 18†

*$p<0.01$ between 0 and 30, 45, 60, 75, 90 minutes.
†$p<0.01$ between control and paraplegic or quadriplegic subjects.

TABLE 5

EFFECT OF INSULIN-INDUCED HYPOGLYCEMIA ON PLASMA CORTISOL LEVELS (ng/100 ml)

Subjects (Number)	Time After Insulin Administration (min)					
	0	30	45	60	75	90
Control (9)	12.4 ± 0.8	13.5 ± 1.3	22.0 ± 3.2*	31.0 ± 5.9*	29.0 ± 3.3*	24.7 ± 3.0*
Paraplegic (6)	12.5 ± 1.4	13.0 ± 2.3	15.8 ± 1.2	21.8 ± 2.6*	21.2 ± 2.2*	18.2 ± 2.2*
Quadriplegic (9)	8.0 ± 1.0†	8.7 ± 1.1†	13.2 ± 1.3†	16.8 ± 2.3*†	17.3 ± 2.4*†	16.6 ± 2.4*†

*$p<0.01$ between 0 and 30, 45, 60, 75, and 90 minutes.
†$p<0.01$ between control and paraplegic or quadriplegic subjects.

Naftchi et al. Peptides. 1985;6 Suppl 1:85-94.

Increased dextrose requirements…

- D10 withdrawn, NPO, q1 hour accuchecks
- Critical sample obtained

	Ref. Range	11/24/2016 23:34
Glucose, Ser/Plasma	Ref Range: 60 - 99 mg/dL	45 (L)
Beta-Hydroxybutyrate	Ref Range: <0.30 mmol/L	0.10
PROINSULIN PLASMA	Ref Range: 3-20	19
C-Peptide	Ref Range: 0.3 - 2.35 pmol/mL	0.54
Cortisol	Units: ug/dL	12.4
Insulin	Ref Range: 2.6 - 24.9 mcU/mL	2.9

Critical Sample Interpretation

TABLE 3. Patterns of findings during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (*i.e.* Whipple's triad not documented) and in individuals with hyperinsulinemic (or IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms

Symptoms, signs, or both	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (nmol/liter)	Proinsulin (pmol/liter)	β-Hydroxybutyrate (mmol/liter)	Glucose increase after glucagon (mg/dl)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	≫3	≫0.2[a]	≫5[a]	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF[b]
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

Neg, Negative; Pos, positive; PGBH, post gastric bypass hypoglycemia.

[a] Free C-peptide and proinsulin concentrations are low.

[b] Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio.

Cryer et al. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.

Additional Labs

- Cosyntropin stimulation test:
  - Cortisol 12.1 → 18.5 → 20.3
- Insulin antibody – negative
- Hypoglycemic agent screen – negative

What would you recommend next?

MRI upper abdomen wwo

PANCREAS: Limited evaluation due to motion artifact. Within the limitations of this exam on pancreatic mass is identified. There is no pancreatic ductal dilation.

BOWEL, MESENTERY: Generalized colonic dilation is similar to previous CT and is compatible with the history of *ovary* syndrome.

IMPRESSION:

1. Limited exam with no evidence of pancreatic lesion
2. Persistent massive colonic dilation compatible with the patient's history of *overuse* syndrome.

What next?

Back to med list…

Bactrim associated with hypoglycemia in case reports

MEDICATIONS

Continuous:

• dextrose 10% / 0.9% NaCl		1,000 mL (11/25/16 1706)

Scheduled Meds:

• aspirin	81 mg	Oral
• dantrolene	50 mg	Oral
• dextrose		
• dextrose		
• heparin	5,000 Units	Subcutaneous
• [START ON 11/26/2016] HEXAVITAMIN	1 Tab	Oral
• [START ON 11/26/2016] multivitamin with minerals (THERAGRAN-M)	1 Tab	Oral
• piperacillin-tazobactam (ZOSYN) 4.5 g in Sodium Chloride 0.9% 50 mL (Minibag)	4.5 g	Intravenous
• sodium chloride	0.5-10 mL	Intravenous
• sulfamethoxazole-trimethoprim-DS	2 Tab	Oral

PRN Meds:

• acetaminophen	650 mg	Oral
• bisacodyl	10 mg	Rectal
• dextrose	25 g	Intravenous Push
• sodium chloride	0.5-10 mL	Intravenous

TABLE 2. Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia (24)

Moderate quality of evidence (⊕⊕⊕◯)
- Cibenzoline
- Gatifloxacin
- Pentamidine
- Quinine
- Indomethacin
- Glucagon (during endoscopy)

Low quality of evidence (⊕⊕◯◯)
- Chloroquineoxaline sulfonamide
- Artesunate/artemisin/artemether
- IGF-I
- Lithium
- Propoxyphene/dextropropoxyphene

Very low quality of evidence (⊕◯◯◯)

Drugs with >25 cases of hypoglycemia identified
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor antagonists
- β-Adrenergic receptor antagonists
- Levofloxacin
- Mifepristone
- Disopyramide
- Trimethoprim-sulfamethoxazole
- Heparin
- 6-Mercaptopurine

Drugs with <25 cases of hypoglycemia identified (see Ref. 24)

Cryer et al. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.

Drug Induced Hypoglycemia

- Systematic review identified 448 publications related to 164 drugs causing hypoglycemia
- Majority were case reports or single cohort studies
- In 39% of publications patients had at least one confounder

TABLE 1. Drugs with low to moderate quality of evidence supporting association with hypoglycemia

	No. of studies	No. of cases	Clinical Setting
Drugs with moderate-quality evidence (⊕⊕⊕◯)			
Cibenzoline	16	16	Chronic and acute: few had diabetes and renal insufficiency
Clinafloxacin	2	16	Acute: pneumonia and sepsis
Gatifloxacin	18	234	Acute: various infections
Glucagon	1	30	Chronic: endoscopy patients
Indomethacin	3	43	Chronic: infants with patent ductus arteriosus
Pentamidine	29	330	Acute: infections in immunocompromised host
Quinine	30	326	Acute: malaria and cerebral malaria
Drugs with low-quality evidence (⊕⊕◯◯)			
Artesunate/artemisin/artemether	4	45	Acute: malaria and cerebral malaria
Chloroquineoxaline sulfonamide	4	20	Chronic: malignancy (mainly lung and colon)
IGF-I	6	65	Chronic: diabetes or isolated GH deficiency
Lithium	3	9	Chronic: postglucose hypoglycemia
Propoxyphene and dextropropoxyphene	10	19	Chronic: renal insufficiency, few had diabetes

Hypoglycemia was symptomatic except in 1 of 16 patients treated with cibenzoline, 2 of 309, pentamidine; 1 of 326, quinine; 1 or 65, IGF-I; and 2 of 9, lithium. The number of + signs (out of possible 4) indicates very low, low, moderate, and high quality evidence, respectively.

Murad et al. J Clin Endocrinol Metab. 2009 Mar;94(3):741-5.

What about Bactrim?

Severe and protracted hypoglycaemia associated with co-trimoxazole use

Elizabeth L Strevel, Ayelet Kuper, Wayne L Gold

Co-trimoxazole (trimethoprim-sulfamethoxazole) is a commonly prescribed antimicrobial agent. Although it is well tolerated in most patients, serious adverse events related to its use have been described. Hypoglycaemia is a rare but potentially life-threatening complication of therapy. We describe a case of refractory hypoglycaemia complicated by seizure associated with co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia in a patient with AIDS. We also review 13 previously reported cases of co-trimoxazole-induced hypoglycaemia. Among this patient population, renal insufficiency was the most prevalent predisposing risk factor (93%). The mean daily dose of co-trimoxazole was 4·5 double strength (160 mg trimethoprim/800 mg sulfamethoxazole) tablets per day. Serum insulin levels were raised or inappropriately normal in 88% of cases in which they were measured, suggesting a sulfonylurea-like effect of co-trimoxazole as the mechanism of hypoglycaemia. All cases required intravenous glucose administration, and 43% experienced protracted (>12 hours) hypoglycaemia. Dosage adjustments should be made when prescribing co-trimoxazole to patients with renal dysfunction.

- Review and case series: 14 cases of trimethoprim-sulfamethoxazole related hypoglycemia
- Impaired renal function in 93% of patients
- Insulin levels elevated or inappropriately normal in 88% of cases, c-peptide elevated in all cases where it was measured

Strevel et al. Lancet Infect Dis. 2006 Mar;6(3):178-82.

Mechanism

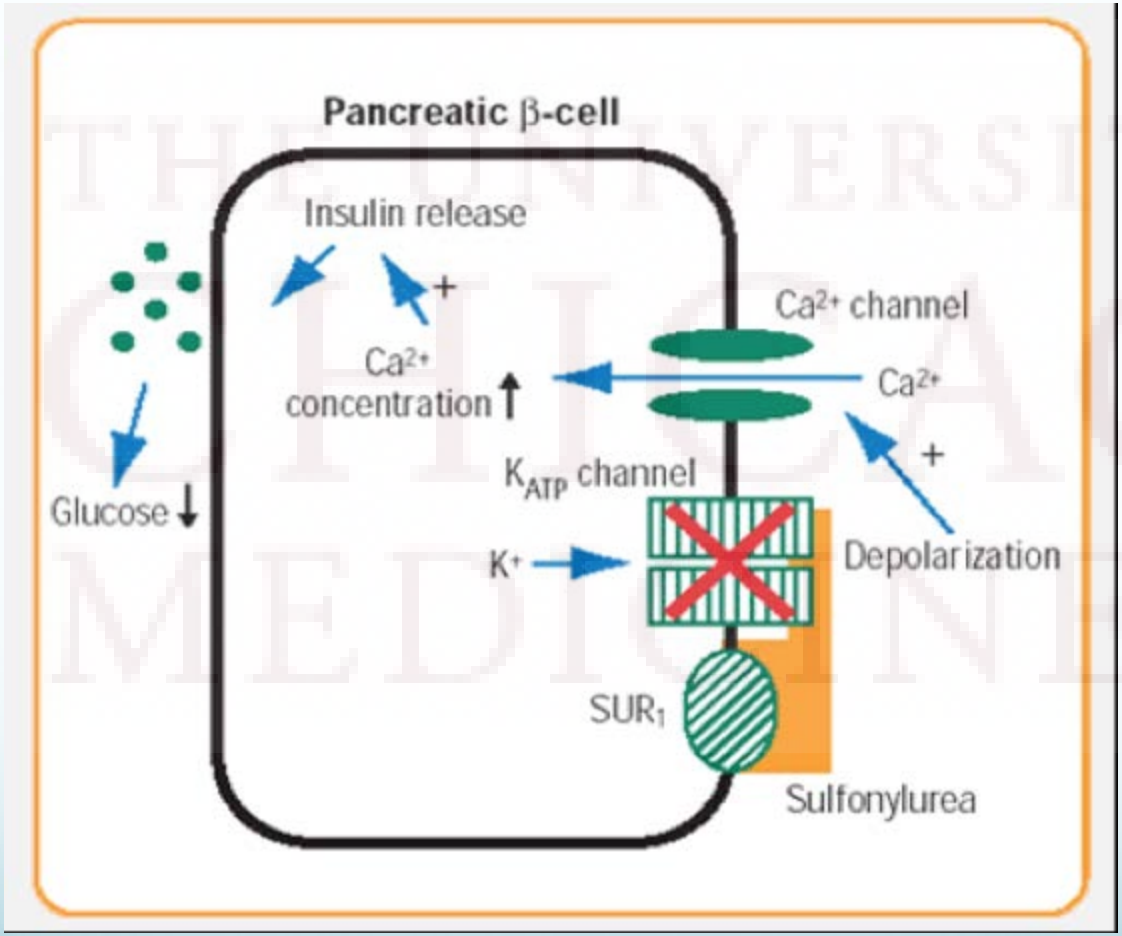
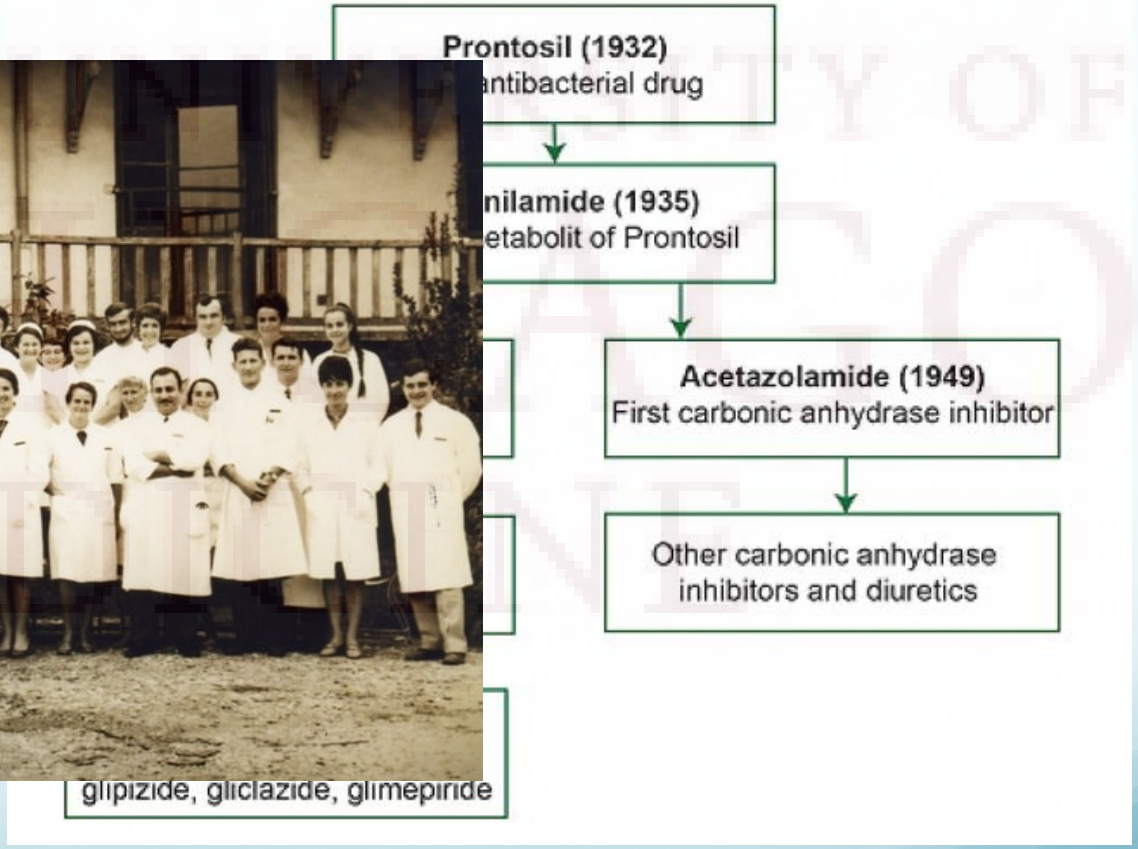


Image Source: https://pedclerk.bsd.uchicago.edu/page/sulfonylurea-poisoning

History of Sulfonylureas



http://www.diapedia.org/management/8104336183/history-of-the-sulphonylureas

Chart review

	Glucose, Ser/Plasma
Ref. Range	Latest Ref Range: 60 - 99 mg/dL
11/1/2004 0237	43 ▼
11/1/2004 0526	89
11/1/2004 1402	134 ▲
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11/2/2004 0628	102
11/2/2004 1357	137 ▲
11/3/2004 0420	91
11/4/2004 0600	79
11/4/2004 2200	89
11/5/2004 2203	93
11/6/2004 2213	97
10/13/2014 1150	76
10/14/2014 0630	71
10/15/2014 0448	96
4/7/2015 1359	100
4/7/2015 1744	98
12/31/2015 1320	112 ▲
12/31/2015 2225	101
1/1/2016 0557	92
11/4/2016 2051	105 * ▲
11/5/2016 2031	52 * ▼
11/6/2016 0637	40 * ▼
11/7/2016 0825	107 * ▲
11/7/2016 1651	129 * ▲
11/8/2016 0417	111 * ▲
11/8/2016 1715	79 *
11/9/2016 0651	87 *
11/9/2016 1701	87 *

- 11/2004 – admitted with pyelonephritis and bacteremia -> Zosyn, Flagyl -> Cipro
- 11/5/16 – sepsis from prostatitis -> Vancomycin, Zosyn -> Ceftazidime -> Cipro, Bactrim

Clinical Course

- Bactrim held
- ID consulted efepime for treatment c
- D10 weaned
- No further h

Objectives

1. Review the causes and evaluation of hypoglycemia in patients without diabetes
2. Understand alterations in the response to insulin-induced hypoglycemia in patients with spinal cord injuries
3. Review medications that can cause hypoglycemia and the associated mechanisms

References

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