Propofol: How to not MISS PRIS

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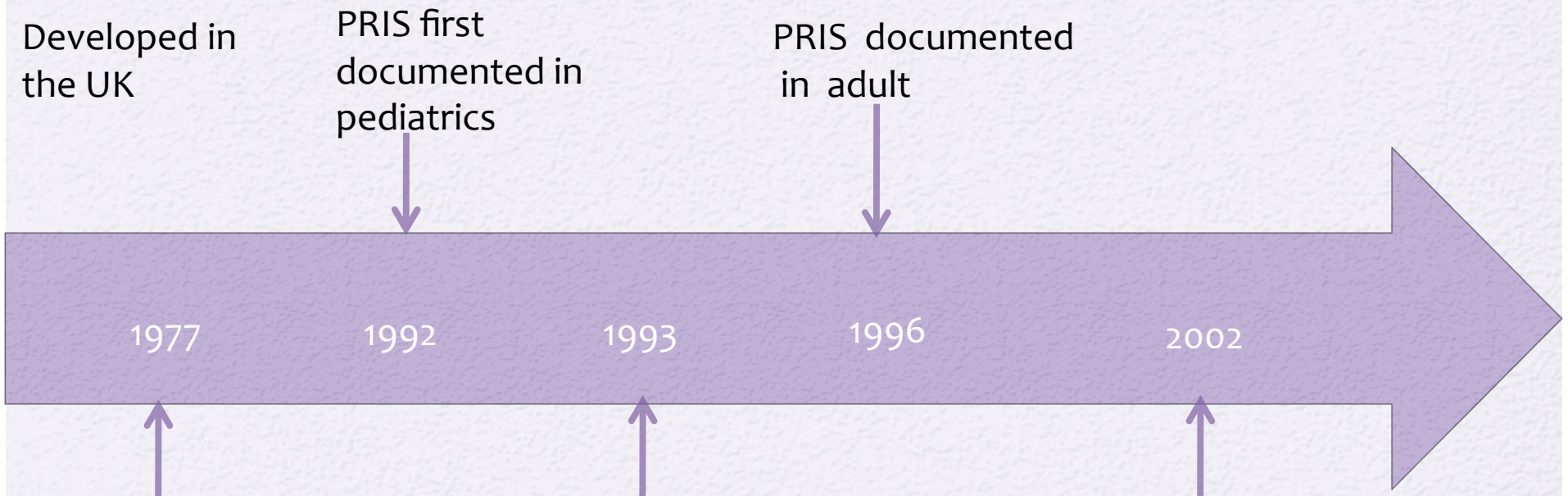
Clinical Practice Guidelines 2013

- Management of Pain, Agitation, and Delirium in Adult Patients in the **Intensive Care Unit**

  - Choice of sedative
    - We suggest that sedation strategies using nonbenzodiazepine sedatives (either **propofol** or dexmedetomidine) may be preferred over sedation with benzodiazepines (+2B).

Crit Care Med 2013; 41:263–306

Propofol timeline



Health Canada
Wikipedia
Pharmacotherapy. 2008;28(2)

Propofol related infusion syndrome (PRIS)

- A cardiovascular and metabolic derangement presenting with variable signs and symptoms
  - worsening metabolic acidosis
  - arrhythmias
  - hypotension with increasing vasopressor requirements
  - acute kidney injury
  - hyperkalemia
  - rhabdomyolysis
  - liver dysfunction
  - hypertriglyceridemia

Crit Care Med 2013; 41:263–306

PRIS: Etiology

- Mitochondrial dysfunction
- Impaired fatty acid oxidation
- Diversion of carbohydrate metabolism to fat substrates
- Propofol metabolite accumulation

Intensive Care Med. 2003 Sep;29(9):1417-25

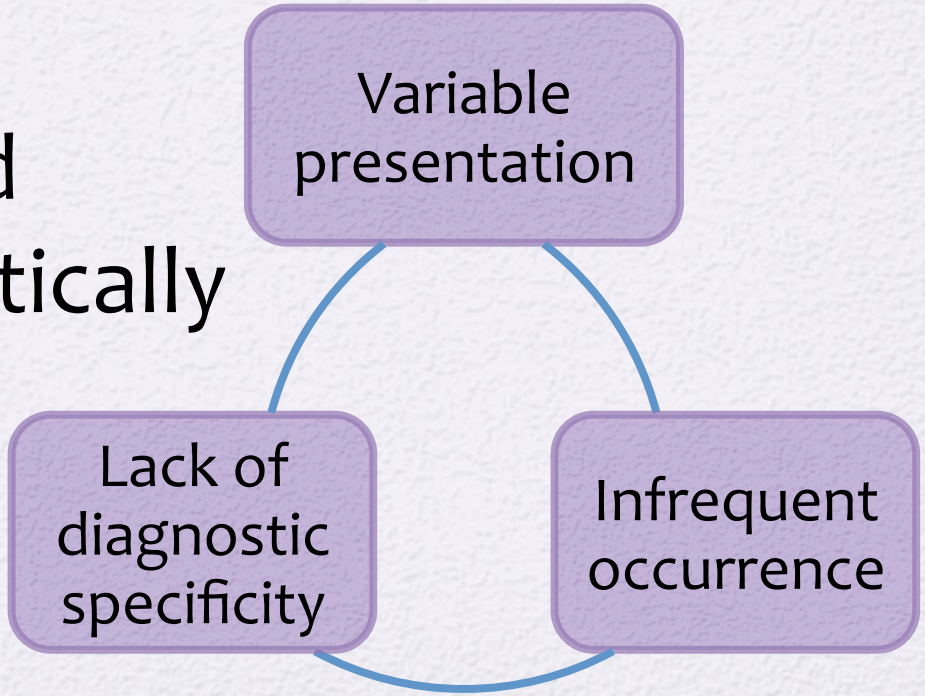
PRIS: Risk factors

- Clinical conditions that result in distributive cardiovascular failure
  - hypoperfusion and/or hypoxemia
- Prolonged administration >48 hours
- High propofol doses (> 70 µg/kg/min)
  - has occured with low-dose infusions

Pharmacotherapy. 2008;28(2)

Prevention

- Management = supportive care
- Mortality = up to 33%
- Early recognition and discontinuation is critically important



Crit Care Med. 2013;41:263–306

Clinical Question

P	Critically ill adults
I	Screening tools for patients on Propofol infusion >60 min
C	Routine care
O	Identification of PRIS Prevention progression of PRIS Mortality

Databases	Medline, Cochrane, Clinical trials.gov, Google Scholar, IPA, Web of Science, EMBASE
Terms	Propofol infusion syndrome, prevention, screening, monitoring, diagnosis, surveillance
Limits	Clinical trial, humans, English, adults Excluded: Case reports
Results	**Prospective** Injury, Int. J. Care Injured 2014 Critical Care 2009 Abstract: Critical Care 2013 **Retrospective** Crit Care Med 2008 THE LANCET 2001 Heart Rhythm 2006 Neurocrit Care 2009

P391

Pre-PRIS? Prospective monitoring for early markers of propofol infusion syndrome

M Stovell, S Smith, M Udberg, W Loh, P Nair

Walton Centre Neurology & Neurosurgery, Liverpool, UK

Critical Care 2013, **17(Suppl 2):**P391 (doi: 10.1186/cc12329)

Stovell M et al, 2013

Prospective observational n=54

Patients	Propofol sedated patients
Methods	4 month period monitored Infusion rate, creatine kinase, triglycerides, creatinine, lactate, pH and base deficit
Definition (Pre-PRIS)	CPK ≥320 mmol/L that had doubled from baseline TG ≥1.7 IU/L

Stovell M et al, 2013

Table 1 (abstract P391)

	Total	Trauma	Nontrauma
≥24 hours infusion	50	34	16
↑CK + ↑TG ≥3.4	6	6	0
↑CK + ↑TG ≥1.7	5	3	2

- Significant CK rise in 11 (22%) of patients
- Pre-pris developed day 2 to 6, mean dose 2.2 mg/kg/hr
  - Mean dose in patients not meeting criteria was 2.0 mg/kg/hr
- No patients developed PRIS

Stovell M et al, 2013

- Authour's conclusions
  - Paired rise in CK and TG represents a pre-pris state that is at risk of developing into full PRIS
- Summary
  - Abstract only
  - No one developed PRIS
  - **Bottom line: given the incidence of PRIS, in a sample of 54 patients it can not be concluded that discontinuing propofol in this scenario impacts development of PRIS**

Injury, Int. J. Care Injured 45 (2014) 245–249

Contents lists available at SciVerse ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Propofol infusion syndrome: A lethal condition in critically injured patients eliminated by a simple screening protocol

Thomas J. Schroeppel [a,*], Timothy C. Fabian [a], L. Paige Clement [b], Peter E. Fischer [c], Louis J. Magnotti [a], John P. Sharpe [a], Marilyn Lee [b], Martin A. Croce [a]

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Schroeppel TJ et al, 2014

Before and after observational study

	Retrospective n=207	Prospective n=1038
Inclusion	Trauma patients in 2005 Propofol >24 hr	Screening Protocol 2006 to 2011 Propofol restricted to TBI
Case identification	≥2 of 1) cardiac arrhythmia or collapse, (2) metabolic acidosis, (3) rhabdomyolysis, and (4) acute kidney injury	
Methods	Compared cases to non cases	Propofol d/c if CPK ≥5000 U/L or lactate ≥4.0 mmol/L
Objective	Syndrome identification and case definition	To test whether screening tool decreased incidence

Schroeppel: retrospective cohort

6 (2.9%) developed PIS

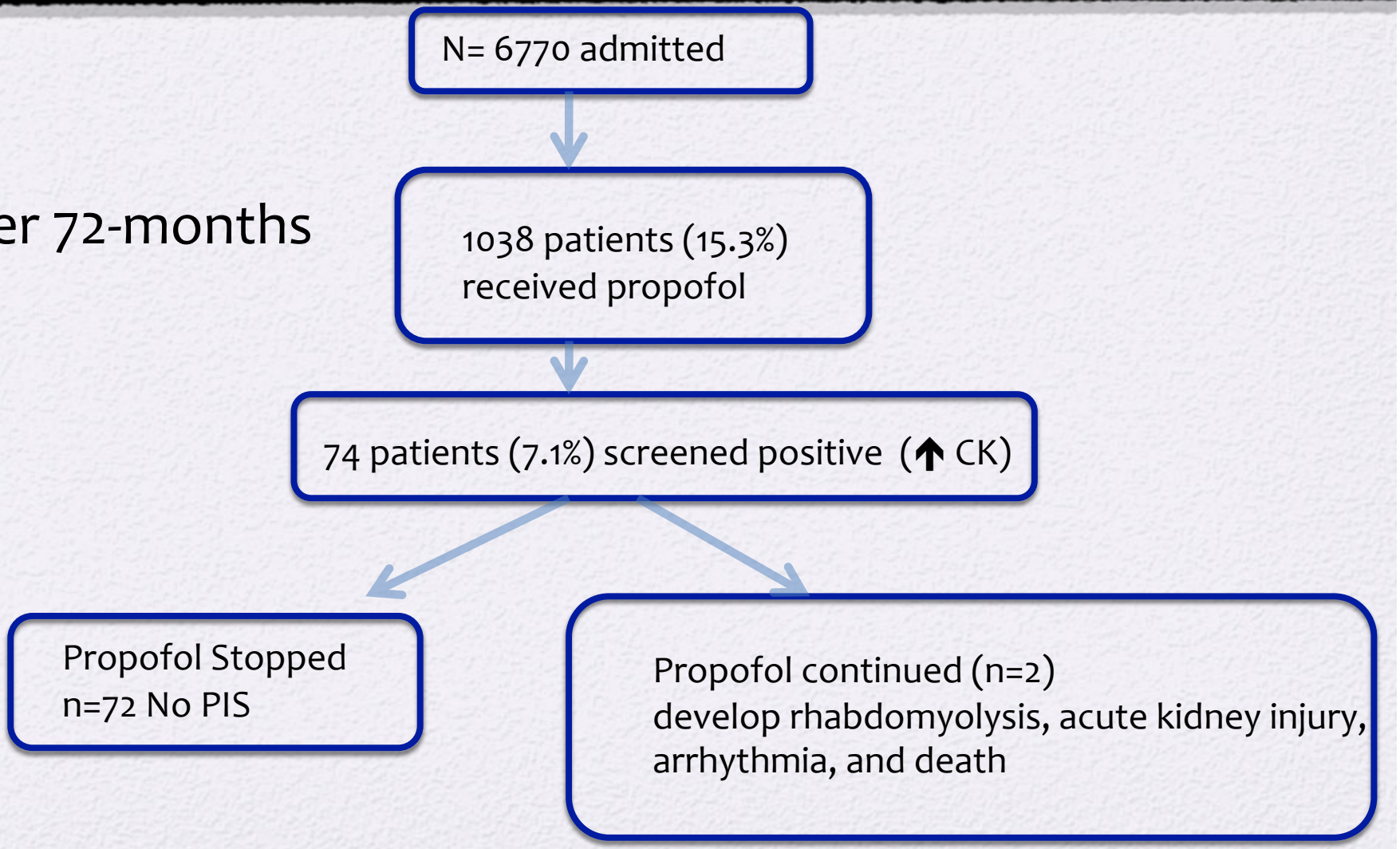
	PIS	No PIS	*p*
Creatinine (mg/dL)	4.3 (3.6)	1.1 (0.4)	0.005
CPK (U/L)	59,871 (95,324)	520 (788)	0.002
Lactate (mmol/L)	3.2 (1.4)	3.1 (2.8)	0.82

Propofol usage comparing PIS and No PIS During Phase I.

	PIS	No PIS	*p*
Total dose (mg)	50,350 (34,180)	9770 (19,420)	0.001
Mean rate ($mg\,kg^{-1}\,h^{-1}$)	2.2 (0.75)	2.1 (1.6)	0.82
Maximum rate ($mg\,kg^{-1}\,h^{-1}$)	32.0 (15)	30.0 (20)	0.45
Total infusion time (h)	413 (262)	65 (115)	0.001

Schroeppel: phase 2

Over 72-months



Schroeppel: conclusion

- Ten-fold reduction in the incidence of PRIS ($p < 0.001$)

Phase I	Phase II
2.9% (6/207)	0.19% (2/1038)

- No difference in Mortality

Authour's Conclusion:

Following implementation of the screening protocol, we have nearly eliminated PIS

Schroeppel: Summary

- Role of increased awareness of propofol infusion syndrome/product monograph limits on dosing
  - Dose and duration of propofol in phase II not reported
- Decreased propofol exposure time
- Adequate sample size to detect PRIS
- **<u>Bottom line</u>: in this prospective cohort discontinuing propofol when CK ≥ 5000U/L eliminated the development of PRIS**

Research

Open Access

Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study

Russel J Roberts[1], Jeffrey F Barletta[2], Jeffrey J Fong[3], Greg Schumaker[4], Philip J Kuper[5], Stella Papadopoulos[6], Dinesh Yogaratnam[7], Elise Kendall[8], Renee Xamplas[9], Anthony T Gerlach[10], Paul M Szumita[11], Kevin E Anger[11], Paul A Arpino[12], Stacey A Voils[13], Philip Grgurich[6], Robin Ruthazer[14] and John W Devlin[15]

Critical Care 2009, **13**:R169 (doi:10.1186/cc8145)

Roberts RJ et al, 2009

Multicenter, prospective observational n=1017

Patients	Admitted to ICU Propofol ≥ 24 hours Median age 57, mostly male
Definition	metabolic acidosis and cardiac dysfunction along with ≥ 1: rhabdomyolysis, hypertriglyceridemia or renal failure
Objective	1. Identify the incidence of PRIS 2. Determine the frequency by which individual PRIS clinical manifestations and risk factors occur

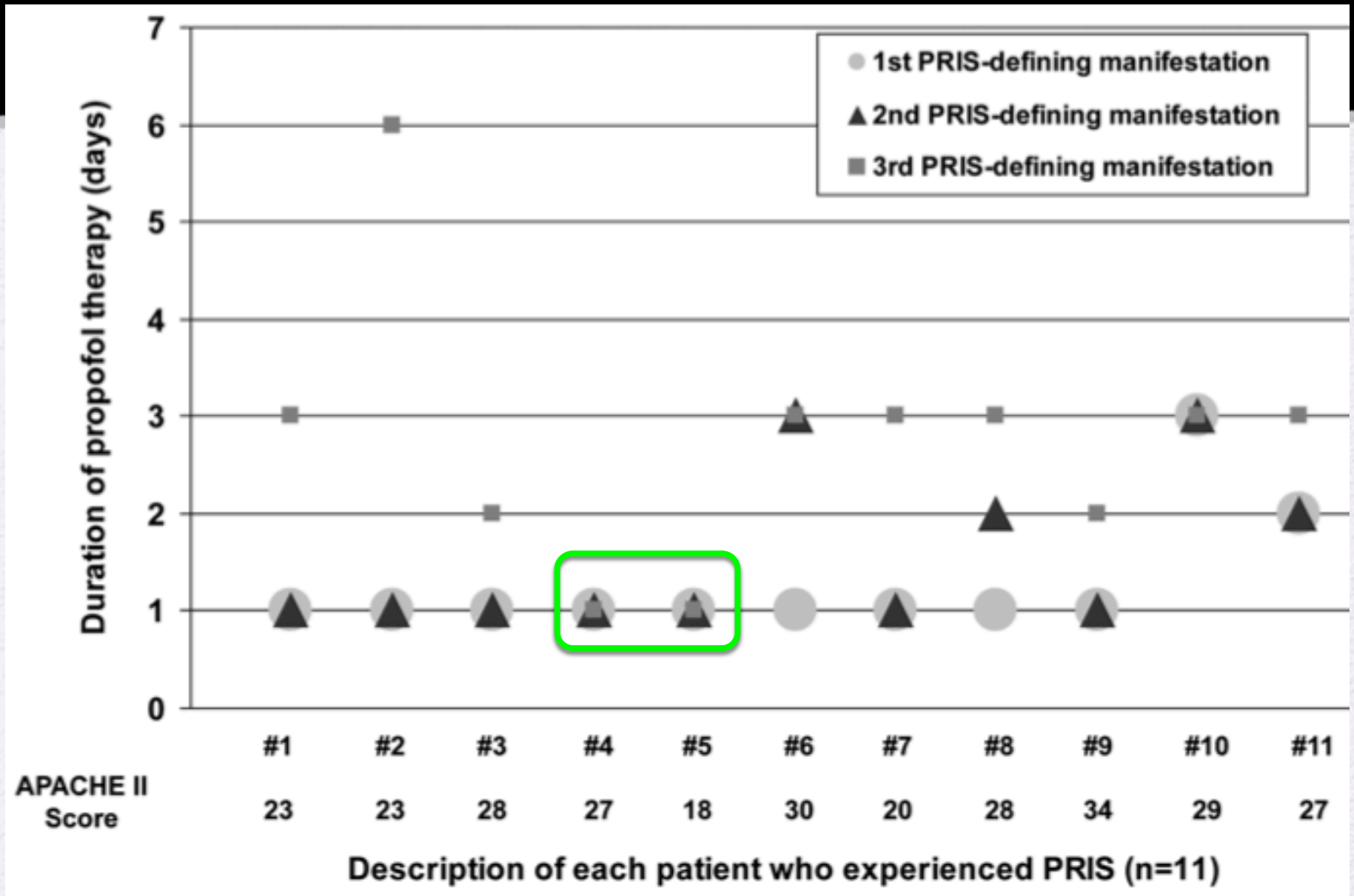
Roberts: Case definition

renal failure	Oliguria, anuria, ↑ SrCr, ↑K
rhabdomyolysis	CPK ≥ 10,000 IU/L
hypertriglyceridemia	TG> 4.5 mmol/L
metabolic acidosis	pH < 7.30 + HCO3< 18 mg/dL
cardiac dysfunction	Brugada-like ECG pattern asystole PEA Vfib, Vtach >30 sec myocardial failure (EF< 40%) bradycardia (heart rate < 50 bpm)

Roberts RJ et al, 2009

- Incidence of PRIS 1.1% (11/1017)
  - 18% (2/11) patients died
- 18% (2/11) received > 83 mcg/kg/min
- Metabolic acidosis, cardiac dysfunction and renal failure =definition in all cases
  - No patients developed rhabdomyolysis
  - No patients developed Brugada-like ECG pattern
  - One developed hypertryglyceridemia

Roberts RJ et al, 2009



Roberts RJ et al, 2009

- Author's Conclusion
  - The incidence of PRIS in a heterogeneous
  - population of critically ill adults prescribed propofol for more than 24 hours is approximately 1% and can occur soon after the initiation of propofol therapy and at low doses

Roberts: Summary

- Ideal trial:
  - all comers, patients admitted to the ICU and sedated on propofol vs alternative agent
- Drug not necessarily stopped
- Not mentioned if the symptoms went away if the drug was stopped
- **<u>Bottom line</u>: some evidence that features consistent with PRIS may be present at low doses and within the first day**

Predictors of mortality in patients with suspected propofol infusion syndrome

Jeffrey J. Fong, PharmD, BCPS; Lynne Sylvia, PharmD; Robin Ruthazer, MPH; Greg Schumaker, MD; Marisol Kcomt, PharmD; John W. Devlin, PharmD, BCPS, FCCM, FCCP

Crit Care Med 2008 Vol. 36, No. 8

Fong JJ et al, 2008

Retrospective, database analysis, n=1139 suspected PRIS cases

Patients	–Reports of patients experiencing ≥1 of 24 published propofol infusion syndrome manifestations –Received propfol for indications other than non procedural sedation –All ages –1989 through 2005
Objective	1) identify predictors of mortality who had PRIS-associated clinical manifestations 2) propose a simple scoring system to identify patients with suspected PRIS who are at ↑ risk of death

Demographic Variable	All Cases (n = 1139)	Died (n = 342)	Survived (n = 797)	p^a
Age				
Adult (≥18 yrs)	817 (80)	222 (71)	595 (85)	<0.0001
Pediatric (<18 yrs)	199 (20)	92 (30)	107 (15)	
	NR: 123 (11)			
Gender				
Female	511 (47)	138 (42)	373 (49)	0.0256
Male	584 (53)	194 (58)	390 (51)	
	NR: 44 (4)			
Type of report				
Expedited	960 (84)	285 (83)	675 (85)	0.461
Periodic	57 (5)	15 (4)	42 (5)	
Direct	122 (11)	42 (12)	80 (10)	
	NR: 0 (0)			
Source of report				
North America	307 (27)	109 (32)	198 (25)	0.0028
Foreign	546 (48)	168 (49)	378 (47)	
	NR: 286 (25)	65 (19)	221 (28)	
Report source				
Health professional	725 (64)	222 (65)	503 (63)	0.5531
Unknown	410 (36)	118 (35)	292 (37)	
Company representative	0.4 (4)	2 (1)	2 (0.3)	
	NR: 0 (0)			
Role of propofol				
Primary suspected drug	725 (70)	253 (74)	542 (68)	0.1126
Secondary suspected drug	343 (30)	89 (26)	254 (32)	
Concomitant drug	1 (0.1)	0	1 (0.1)	
	NR: 0 (0)			
Manufacturer				
AstraZeneca (Diprivan)	705 (62)	207 (61)	498 (63)	0.0177
Generic	384 (34)	111 (33)	273 (34)	
Other	50 (4)	24 (7)	26 (3)	
	NR: 0 (0)			
Propofol dose				
≥83 μg/kg/min	88 (8)	50 (15)	38 (5)	0.104
<83 μg/kg/min	41 (3)	17 (5)	24 (3)	
	NR: 1010 (89)			
Duration of propofol therapy				
≥48 hrs	74 (7)	26 (8)	8 (0.01)	0.0029
<48 hrs	62 (5)	48 (14)	54 (7)	
	NR: 1003 (88)			
Concomitant use of glucocorticosteroids	111 (10)	37 (11)	74 (9)	0.424

342 (30% fatal)

NR 88%

Crit Care Med 2008 Vol. 36, No. 8

Fong JJ et al, 2008

- Mortality scoring scheme points

Table 5. Multivariable logistic regression model coefficients and mortality scoring scheme points

Term in Model	Beta	se (Beta)	*p*	Score
Rhabdomyolysis	0.7437	0.257	0.0038	1
Metabolic acidosis	1.2395	0.222	<0.0001	1
Cardiac	1.5211	0.168	<0.0001	1
Renal failure	1.0346	0.237	<0.0001	1
Age under 18 yrs	0.8222	0.219	0.0002	1
Rhabdomyolysis and hypotension	1.2977	0.395	0.0010	1

Fong JJ et al, 2008

Table 6. Predicted and observed mortality for each possible point score

Total Mortality Risk Score	Predicted Death % (From Score Model)	Observed Death % (From Database)
0	9.6	9.7 (22/226)
1	23	24 (112/469)
2	47	44 (85/195)
3	72	81 (58/72)
4	88	83 (34/41)

Fong JJ et al, 2008

- Author's Conclusion
  - Identified a number of factors that are independently associated with a higher risk for death in patients with suspected PRIS
  - Rhabdomyolysis, metabolic acidosis, cardiac, renal failure, age <18 years, combo of rhabdomyolysis and hypotension

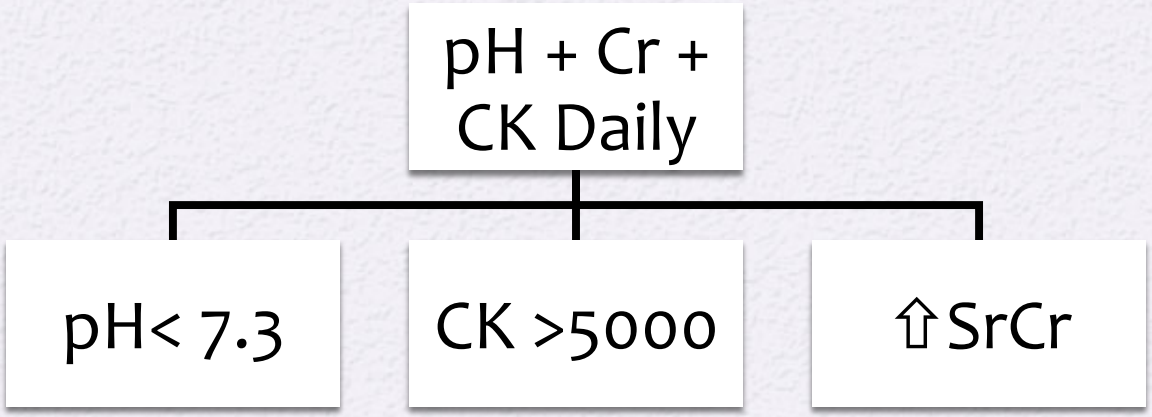
Fong: Summary

- 44% of reports contained the term PRIS
- Indentified covariates that ↑ risk of death
  - We don't know if stopping the drug changes this outcome
  - Or if these covariates are even associated with being on the drug
- Reporting bias
  - rates of mortality are likely inflated →propensity to report when outcomes like mortality occur
- Lack of potential confounders reported to the medwatch program
- **<u>Bottom line:</u> propofol + rhabdomyolysis, metabolic acidosis, cardiac, renal failure or age <18 years, ↑ risk of death. Hepatic abnormalities and dyslipidemia did not.**

Summary

Stovell (2013)	Schroeppel (2014)	Roberts (2009)	Fong (2008)
Abstract Prospective	Before and after observational	Prospective	Retrospective
?	Trauma/TBI	ICU	Adverse event reports in patients received propofol
CK ≥320 TG >1.7	CK ≥ 5000U/L	pH < 7.30 + Cardiac abnormalities + renal failure <83 mcg/kg/min + <24 hours	Rhabdomyolysis, metabolic acidosis, cardiac, renal failure, age<18

Conclusion



Abnormalities explained by clinical scenario?

↓

Change to alternative sedative

Clinical question

- Is there a ~~validated screening tool~~ that I can use to:
  - Identification of PRIS ✔
  - Prevention progression of PRIS **?**
  - Mortality
    - Identify factors associated with mortality ✔

Extras..

PRIS

- 83 published case reports
- Most common first-reported signs of PRIS
  - new-onset metabolic acidosis (86%)
  - cardiac dysfunction (88%)
- The occurrence of other manifestations is less frequent
  - new-onset rhabdomyolysis (45%)
  - renal failure (37%)
  - hypertriglyceridemia (15%)

Critical Care 2009, 13:R169

Schroeppel TJ et al, 2014

Demographics and injury severity all patients.

	Phase I ($n=207$)	Phase II ($n=1038$)	p
Age (years)	29 (22)	33 (26)	0.12
Male	168 (81%)	810 (78%)	0.44
Blunt	186 (90%)	945 (91%)	0.58
ISS	26 (18)	29 (17)	0.10
GCS	8 (11)	7 (9)	0.005
Head AIS	4 (1)	4 (1)	0.11
ADM SBP (mm/Hg)	147 (36)	142 (35)	0.18
ADM HR (beats/min)	102 (37)	102 (37)	0.56
ADM lactate (mmol/L)	2.8 (2.1)	3.2 (2.7)	0.006
ADM BD (meq/L)	3.2 (4.4)	3.4 (5.9)	0.82
Mortality	26 (13%)	138 (13%)	0.82

OBJECTIVES

Cochrane Protocol

1. To identify the propofol dose and duration of infusion associated with the primary outcome (PRIS and cardiac arrest)

2. To describe the patient characteristics associated with the primary outcome

3. To identify a possible association between serious adverse events related to propofol use and the patient care setting (paediatric intensive care, operating room, paediatric emergency or other)

4. To describe the length of time from initiation and ending of propofol infusion to the development of the primary outcome

5. To identify the mode of surveillance for AE in different study designs (active surveillance, passive or specific monitoring procedures for collecting AE) and the relationship with identified AE

Inclusion	Not limited by study design Cochrane recommends non randomized studies for reviews of adverse effects
P	Pediatrics aged 28 days to 19 years Propofol >60 minutes in a hospital (intensive care unit, operating room, emergency room, or any other location within the hospital) or other medical setting
I	Propofol infusion >60 min
C	Standard care and it will include the most common sedative agents used for paediatric sedation.
O	Cardiac arrest Propofol infusion syndrome Defined as: metabolic acidosis, arterial pH ≤ 7.3 along with a serum bicarbonate ≤ 18 mg/dL; plus the presence of any of: 1. rhabdomyolysis 2. hypotension 3. hepatic transaminitis 4. Hypertriglyceridaemia 5. Hypoxia 6. Temp > 38.3 °C 7. cardiac dysfunction 8. renal failure

Cochrane Database of Systematic Reviews 2012