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Clinical Gastroenterology and Hepatology 2014;12:303–307

PANCREAS, BILIARY TRACT, AND LIVER

Aggressive Hydration With Lactated Ringer's Solution Reduces Pancreatitis After Endoscopic Retrograde Cholangiopancreatography

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Overview:

- Pilot study of LR ~3.8 L (n=39) vs. ~2.2 L (n=23)
- Outcome: Post-ERCP Pancreatitis (Hyperamylasemia + Pancreatic Pain)

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Background

- Post-ERCP Pancreatitis occurs in 3.5% of patients and severe pancreatitis 0.4% with a mortality of 0.11% (2007)
- Pancreatitis is treated by hydration
- Limited evidence shows lactated Ringer's (LR) are not clinically inferior to normal saline but may reduce the incidence of SIRS (2011), possibly by not causing metabolic acidosis, and promoting a less inflammatory cascade (2004)

Am J Gastroenterol. 2007 Aug;102(8):1781-8.
Clin Gastroenterol Hepatol. 2011 Aug;9(8):710-717.
Am J Physiol Regul Integr Comp Physiol. 2004 Apr;286(4):

Methods

- ERCP patients computer randomized (2:1)
- LR Rate not concealed to patients or investigators
- Inclusion: Inpatients with a biliary indication without pancreatitis (choledocholithiasis, bile duct leak, and biliary obstruction)
- Exclusion: Acute or chronic pancreatitis, CHF, CKD (CrCl<40), liver dysfunction, respiratory insufficiency, sepsis, hyper/hyponatremia, prior sphincterotomy, age>70

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Interventions

- Aggressive hydration (intervention):

  LR 3 mL/kg/h during the procedure

  + 20 mL/kg bolus immediately after the procedure

  + 3 mL/kg/h for 8 hours

  …then if no pain advanced diet or 1.5 mL/kg/h

- Standard hydration (control):

  LR 1.5 mL/kg/h during the procedure

  No bolus after the procedure

  + 1.5 mL/kg/h for 8 hours

  …if pancreatitis @ 2 h or @ 8 hour, then 20 mL/kg bolus followed by 3 mL/kg/h

- Fluids in both groups stopped when patients tolerated a regular diet

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- Fluids in both groups stopped when patients tolerated a regular diet

EXAMPLE
150 lb patient=68kg

204 mL/h during
+ 1,360 mL bolus
+1,632 mL afterwards
3,196 mL total
(median 3.8 L)

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150 lb patient=68kg

102 mL/h during
+816 mL afterwards
918 mL total
(median 2.2 L)

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Baseline Characteristics

Table 1. Selected Baseline Characteristics

	Standard hydration (N = 23)	Aggressive hydration (N = 39)
Age, *y* (mean ± SD)	45 ± 17	43 ± 14
Comorbidities, n (%)	8 (34.8)	11 (28.2)
Hispanic ethnicity, n (%)	18 (78.3)	34 (78.3)
Indication: bile duct stone, n (%)	17 (73.9)	29 (74.4)
Female gender	13 (56.5%)	19 (48.7%)
Total bilirubin, *mg/dL* (mean ± SD)	4.2 ± 5.9	3.7 ± 3.8
Hematocrit, % (mean ± SD)	36 ± 4	37 ± 5
Creatinine, *mg/dL* (mean ± SD)	0.7 ± 0.2	0.7 ± 0.2

NOTE. $P > .25$ for all comparisons.
SD, standard deviation.

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Baseline Characteristics

Table 2. Risk Factors for Post-ERCP Pancreatitis Based on 2012 American Society for Gastrointestinal Endoscopy Guidelines[7]

	Standard hydration (N = 23)	Aggressive hydration (N = 39)
Normal bilirubin (≤1 mg/dL)	6 (26.1%)	9 (23.1%)
Pancreatic duct injection	4 (17.4%)	10 (25.6%)
Precut sphincterotomy	1 (4.3%)	1 (2.6%)
Young age (<30 y)	3 (13.0%)	4 (10.3%)

NOTE. No patients in either group had prior post-ERCP pancreatitis, suspected sphincter of Oddi dysfunction, pancreatic sphincterotomy, or balloon dilation of the biliary sphincter.
$P > .25$ for all comparisons.

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End Points

- Primary End Point: hyperamylasemia (amylase>3 x ULN) + increased epigastric pain (≥3 points on visual analogue scale) for ≥ 24 h after the procedure
- Secondary End Points:
  - Hyperamylasemia
  - Increased epigastric pain
  - Volume Overload

Table 3. Results in the Study Groups

	Standard hydration (N = 23)	Aggressive hydration (N =39)	
	n *(%)*	n *(%)*	*P* value
Post-ERCP pancreatitis	4 (17)	0 (0)	.016
Hyperamylasemia	9 (39.1)	9 (23.1)	.146
Pancreatic pain	5 (21.7)	5 (7.7)	.116
	Median (IQR)	Median (IQR)	*P* value
2-Hour amylase (*U/L*)	172 (596)	162 (296)	.42
8-Hour amylase (*U/L*)	200 (639)	138 (190)	.10
Total fluids during first 24 hours (*L*)	2.2 (2.1)	3.8 (1.5)	<.001
Hospitalization (*days*)	4 (6)	(3)	.41

IQR, interquartile range.

None of the patients developed clinical evidence of fluid overload (edema, ascites, rales, decreased O2 saturation at 2, 8 or 24 hours)

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Discussion

- Small, unconcealed, unblinded, regional (78% Hispanic)
- Unexpectedly high rate of post-ERCP pancreatitis in the control group (17%, n=4/23)
- While more data is needed, given the plausible basic science mechanism and low risk of hydration in patients at low-risk for volume overload, aggressive hydration should be strongly considered to prevent post-ERCP Pancreatitis
- LR: 3 mL/kg/h during the procedure + 20 mL/kg bolus immediately after the procedure + 3 mL/kg/h for 8 hours

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Tobacco Smoking Cessation and Improved Gastroesophageal Reflux: A Prospective Population-Based Cohort Study: The HUNT Study

Eivind Ness-Jensen, MD[1,2], Anna Lindam, MSc[3], Jesper Lagergren, MD, PhD[3,4] and Kristian Hveem, MD, PhD[1]

OBJECTIVES: **Tobacco smoking increases the risk of gastroesophageal reflux symptoms (GERS), but whether tobacco smoking cessation improves GERS is unclear. The aim of this study was to clarify if tobacco smoking cessation improves GERS.**

METHODS: **The study was based on the Nord-Trøndelag health study (the HUNT study), a prospective population-based cohort study conducted from 1995–1997 to 2006–2009 in Nord-Trøndelag County, Norway. All residents of the county from 20 years of age were invited. The study included 29,610 individuals (61% response rate) who reported whether they had heartburn or acid regurgitation. The association between tobacco smoking cessation and improvement in GERS was assessed by logistic regression, providing odds ratios (ORs) with 95% confidence intervals (CIs). The analyses were stratified by antireflux medication, and the results were adjusted for sex, age, body mass index (BMI), alcohol consumption, education, and physical exercise. Subgroup analyses were also stratified by BMI.**

RESULTS: **Among individuals using antireflux medication at least weekly, cessation of daily tobacco smoking was associated with improvement in GERS from severe to no or minor complaints (adjusted OR 1.78; 95% CI: 1.07–2.97), compared with persistent daily smoking. This association was present among individuals within the normal range of BMI (OR 5.67; 95% CI: 1.36–23.64), but not among overweight individuals. There was no association between tobacco smoking cessation and GERS status among individuals with minor GERS or individuals using antireflux medication less than weekly.**

CONCLUSIONS: **Tobacco smoking cessation was associated with improvement in severe GERS only in individuals of normal BMI using antireflux medication at least weekly, but not in other individual with GERS.**

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Am J Gastroenterol 2014; 109: 171-177

Background

- Smoking is associated with increased GERD symptoms OR (1.3-2.5 vs. nonsmokers)
- Smoking reduced LES pressure and reduces saliva
- Prior short term studies (24 & 48hours , n=10, n=8, n=14) didn’t show GERD improvement by pH measurement with brief smoking cessation

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Methods

- Nord-Trodelag Health Study (HUNT study), a series of survey for the entire population over age 20 of Nord-Trodelag County, Norway.
- 3 Surveys (1984-86, 1995-97, 2006-08)
- Q: "*To what degree have you had heartburn or acid regurgitation during the previous 12 months?*" (previously validated question)
- A: "No complaints," "Minor Complaints," or "Severe Complaints.

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Methods: Study Outcome (GERD)

- From the 1995-97 survey until the 2006-08 survey
  - **Changing** "Severe" to "No" or "Minor" Complaints:
    Study Outcome
  - **Staying** "Severe" during both Surveys:
    Reference

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Methods: Smoking Cessation

- Smoking question:
  - 1995-1997 survey: 4 yes/no questions
    - "Have you ever smoked daily?
    - "Do you smoke… cigarettes daily? ...cigars daily? … pipe daily?"
  - 2006-08 survey:
    - Q: "Do you smoke?"
    - A: 1. "No, I have never smoked" 2. "Yes, cigarettes occasionally (parties/vacation)" 3. "Yes, cigarettes daily."
  - Those who **Quit** from '95 to '06 OR **Reduced** to occasionally were defined as **"exposed"** to smoking cessation
  - Those who were persistent daily smokers from '95 to '06 were **"unexposed"** to smoking cessation

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Methods: Other survey variables

- BMI, sex, age, alcohol consumption, education, exercise, antireflux medication
- Antireflux medication included PPI, H2B, AA
- Until 2010 high does H2B and all PPI required Rx, and data was available to the researchers
- Survey included Q: “How often have you used OTC medication against the following complaints during the last month”
  - “Rare/never, 1-2 X weekly, 4-6 X/week, Daily”

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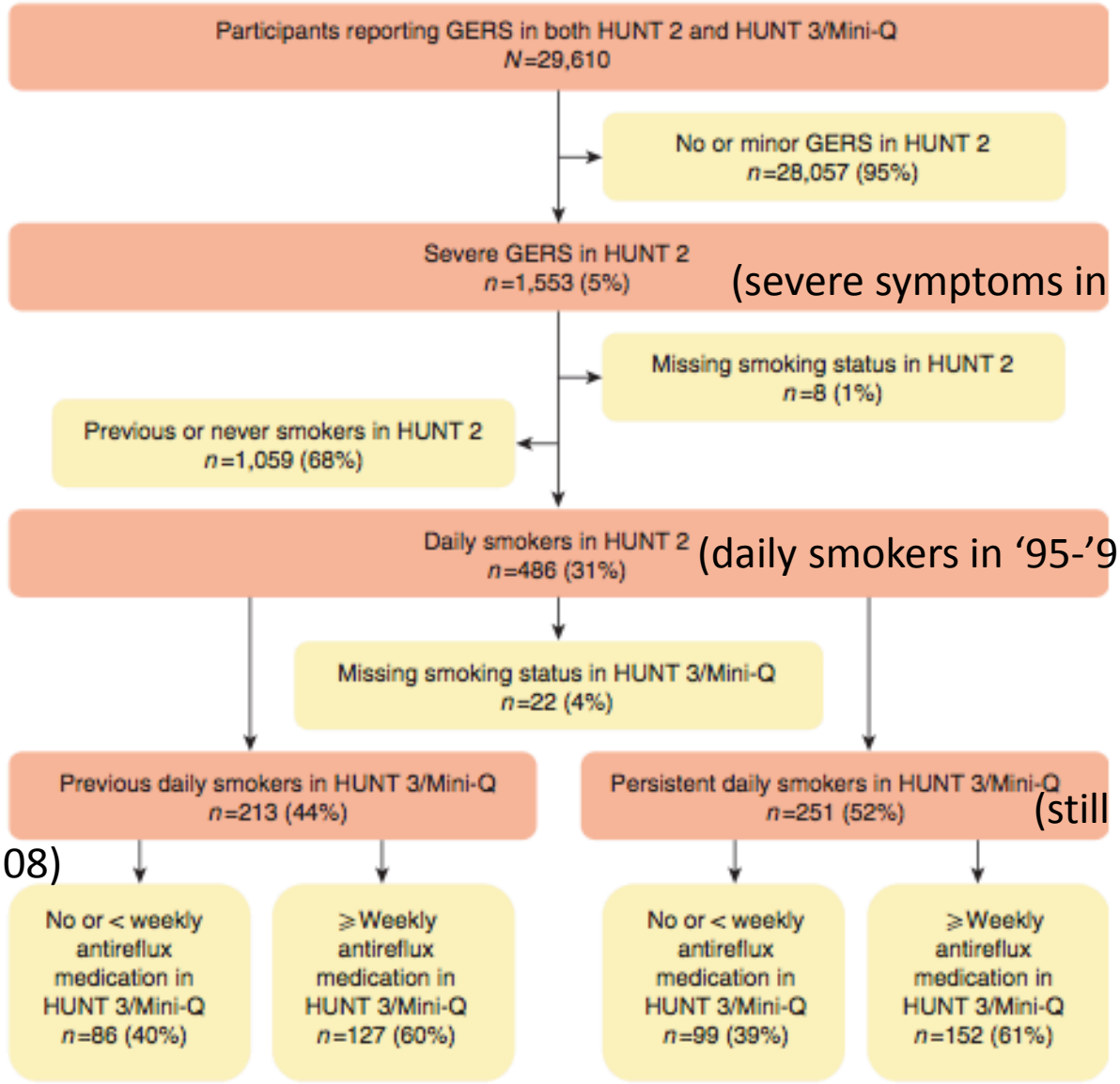

(severe symptoms in '95-'97)

(daily smokers in '95-'97)

(quit or reduced smoking by '06-'08)

(still smoking in '06-'08)

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Methods: Multivariable Logistic Regression

Table 2. OR with 95% CI of improvement in severe GERS by tobacco smoking cessation, stratified by use of antireflux medication[a]

	Unadjusted			Adjusted for sex and age			Fully adjusted[b]		
Antireflux medication[c]	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
No or < weekly	185	1.12	0.48–2.62	185	1.06	0.45–2.52	181	0.95	0.39–2.30
≥Weekly	279	1.44	0.90–2.32	279	1.62	0.99–2.65	268	1.78	1.07–2.97

CI, confidence interval; GERS, gastroesophageal reflux symptoms; HUNT, Nord-Trøndelag health study; OR, odds ratio.

Comparing previous daily smokers with persistent daily smokers as reference.

[a]From severe heartburn or acid regurgitation (GERS) in HUNT 2, to no or minor GERS in HUNT 3/Mini-Q; comparing previous daily smokers with persistent daily smokers as reference.

[b]Adjusted for sex, age, body mass index, alcohol consumption, years of education, and physical exercise.

[c]Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids.

- Without any adjustments, smoking cessation is not significant
- Adjusting for sex, age, BMI, alcohol, education and exercise, there was improvement in GERD symptoms for those who cut down on their smoking and were taking antireflux medication at least weekly

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Methods: Multivariable Logistic Regression

Table 3. OR with 95% CI of improvement in severe GERS by tobacco smoking cessation, stratified by the use of antireflux medication and BMI[a]

		Unadjusted			Adjusted for sex and age			Fully adjusted[b]		
Antireflux medication[c]	BMI (kg/m²)	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
No or < weekly	All	185	1.12	0.48–2.62	185	1.06	0.45–2.52	181	0.95	0.39–2.30
	18.5–24.9	50	1.06	0.21–5.30	50	0.89	0.17–4.65	49	0.80	0.13–5.08
	25.0–29.9	77	1.29	0.33–5.00	77	1.32	0.33–5.27	63	1.13	0.27–4.75
	≥30.0	57	1.04	0.23–4.64	57	0.74	0.14–3.89	57	0.90	0.16–5.17
≥ Weekly	All	279	1.44	0.90–2.32	279	1.62	0.99–2.65	268	1.78	1.07–2.97
	18.5–24.9	50	3.92	1.13–13.60	50	4.70	1.22–18.18	49	5.67	1.36–23.64
	25.0–29.9	124	1.25	0.62–2.56	124	1.20	0.57–2.53	121	1.24	0.57–2.71
	≥30.0	100	1.01	0.46–2.22	100	1.28	0.55–2.99	93	1.29	0.53–3.17

BMI, body mass index; CI, confidence interval; GERS, gastroesophageal reflux symptoms; HUNT, Nord-Trøndelag health study; OR, odds ratio.

[a]From severe heartburn or acid regurgitation (GERS) in HUNT 2, to no or minor GERS in HUNT 3/Mini-Q; comparing previous daily smokers with persistent daily smokers as reference.

[b]Adjusted for sex, age, body mass index, alcohol consumption, years of education, and physical exercise.

[c]Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids.

- Breaking down by BMI shows that the greatest improvement in those who quit smoking and were on antireflux medications >weekly had a BMI 18.5-24.9, even when unadjusted

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Weaknesses

- Norwegian population, observational study
- Subjectivity of GERD symptoms / misclassification
- Loss to follow-up, selection and survival bias

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Conclusions

- Smoking cessation is associated with improvement in severe GERD symptoms in individuals of normal weight using regular antireflux medication.
- "Take the meds, lose the weight and quit the smoking."

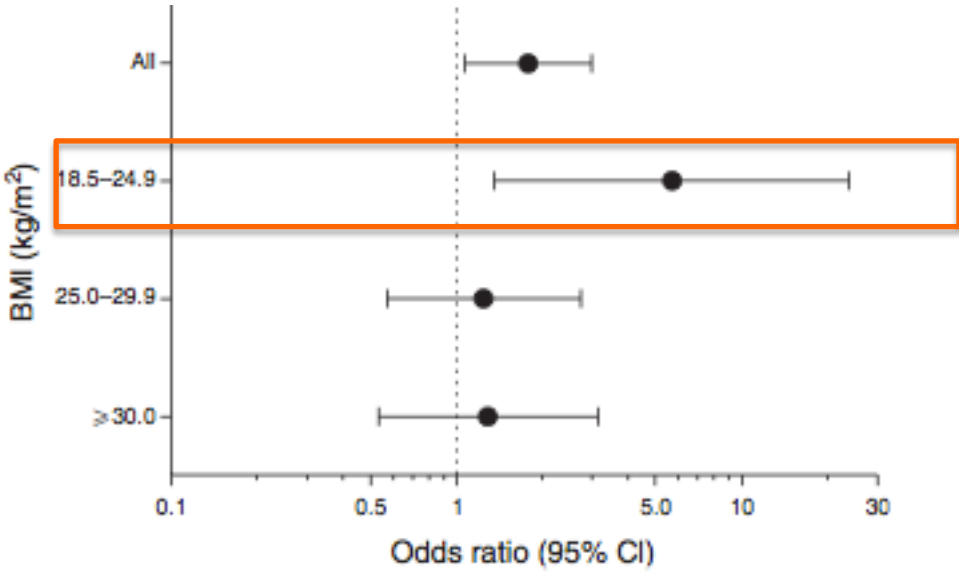

Figure 2. Odds ratio and 95% confidence interval (CI) of improvement in severe gastroesophageal reflux symptoms by tobacco smoking cessation, comparing previous daily tobacco smokers with persistent daily tobacco smokers as reference. Restricted to those using *at least weekly* antireflux medication and stratified by body mass index (BMI). Model adjusted for sex, age, alcohol consumption, education, and physical exercise.

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