

Bicarbonate, Saline, and NAC in the Prevention of Contrast -induced Acute Kidney Injury: An Analysis of the Meta-Analyses

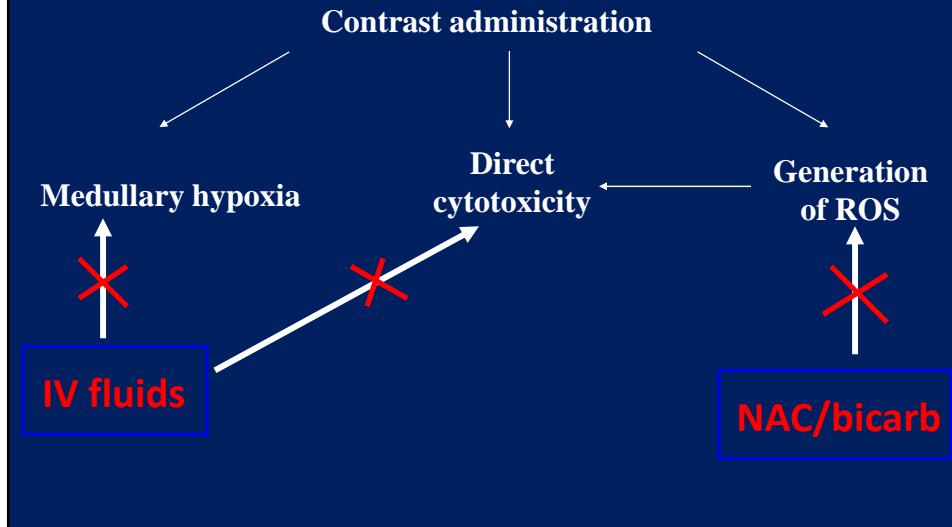
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CIAKI

- **Common cause of AKI**
- **↑ SCr \geq 0.5 mg/dL or 25% w/i 48-72 hrs**
- **Associated with:**
 - Prolonged hospitalization
 - Persistent renal injury/ accelerated CKD
 - Short and long-term mortality
 - ↑ costs (> \$11,800 in 1 yr costs)*
- **Preventable form of AKI**
 - Many procedures scheduled in advance
 - Risk factors easily identifiable

* Subramanian et al. J Medical Economics 2007;10:119-134

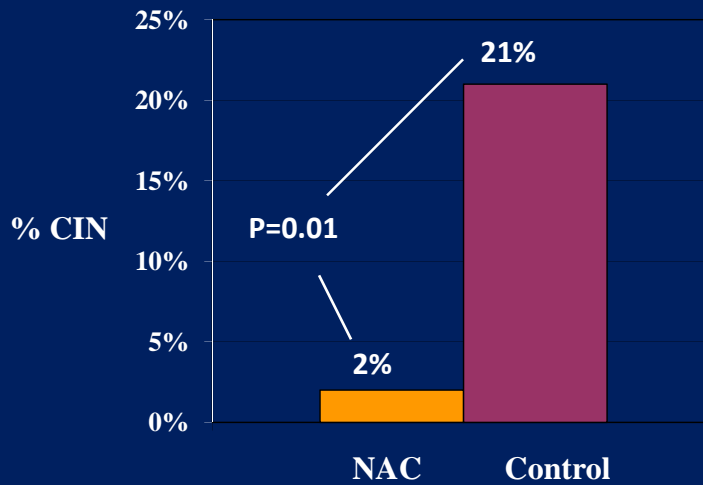
Pathophysiology and prevention



NAC and Bicarbonate

- Biological plausibility to their protective effects
- Multiple clinical trials
 - Small, heterogeneous patient populations
 - Conflicting results
 - Led to meta-analyses of both interventions
- How do we interpret these meta-analyses to inform evidence-based clinical care?

Initial trial on NAC (n=83)



Tepel M, et al. N Engl J Med 2000; 343:180-184

Clinical trials on NAC published in English 2000-2009 (N=26)

- Varying doses – from 1x to 6x over ≥ 1 day
- Varying routes of administration
 - 6 studies used IV
 - 19 studies used PO
 - 1 study used IV and PO
- Varying procedures
 - Coronary angiography
 - Peripheral angiography
 - Computed tomography
- Sample size
 - Smallest = 24 pts
 - Largest = 487 pts
 - 14 (54%) < 100 pts

Clinical trials on NAC published in English 2000-2009

- Anticipated fx size
 - 16 (62%) no anticipated fx size
 - 9 (38%) anticipated fx size > 50%
 - 5 (19%) anticipated fx size = 90%
- Varying results
 - 11 (42%) demonstrated ↓ CIAKI
 - 15 (58%) demonstrated no ↓ CIAKI
- Pt-centered outcomes
 - 16 (62%) tracked short-term need for RRT
 - 6 (23%) tracked death
 - 1 (94%) tracked persistent renal injury/re-hospitalization

Meta-analyses of NAC (N=16)

Positive fx

- Alonso et al. (n=8)
- Birck et al. (n=7)
- Duong et al. (n=14)
- Gawenda et al. (n=28)
- Isenbarger et al. (n=7)
- Liu et al. (n=9)
- Misra et al. (n=5)
- Trivedi et al. (n=16)
- Kelly et al. (n=26)
- Guru et al. (n=11)

Negative/inconclusive fx

- Gonzalez et al. (n=22)
- Kshirsagar et al. (n=16)
- Nallamothe et al. (n=20)
- Zagler et al. (n=13)
- Pannu et al. (n=15)
- Bagshaw et al. (n=14)

Interpreting results of meta-analyses

- How methodologically sound and homogenous are the trials included in the meta-analysis?
- Is there statistical heterogeneity?
- Is there publication bias?

Methodological issues with primary trials of NAC & pooling results

- Enormous clinical heterogeneity
 - Pt populations, procedures, doses and routes of NAC, co-interventions
- Inclusion of lower risk pts
 - Near intact kidney fxn, non-diabetics
- Small sample size based on implausible fx sizes

Statistical heterogeneity

- Measure of whether the variability of results across individual trials is beyond chance alone
- Standard assessment in meta-analysis
- If present, pooling of data may not provide valid conclusions

Statistical heterogeneity in Meta-analyses of NAC

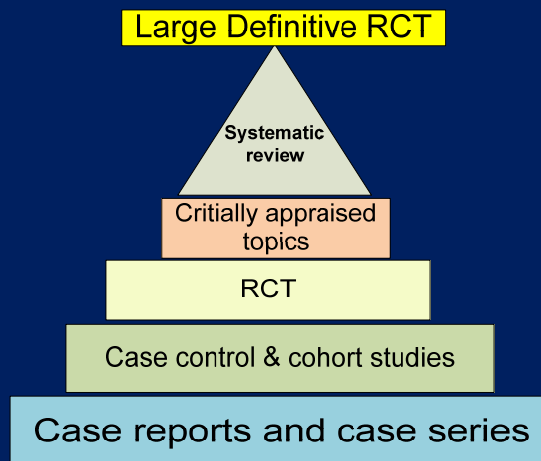
- 11 meta-analyses reported statistically significant heterogeneity in trials
 - 4 studies minimized or did not report on heterogeneity
 - 1 study reported no heterogeneity
- } All 5 of these studies found NAC effective

Publication bias

- ↑ likelihood of publication of studies with positive results compared to results that support the null → can impact the conclusion of pooled results
- Of 16 meta-analyses:
 - 5 reported pub. bias
 - 5 reported no pub. bias
 - 6 did not report on pub. bias

Conclusions of meta-analyses

- 12 of 16 meta-analyses call for future large clinical trials to clarify effect of NAC



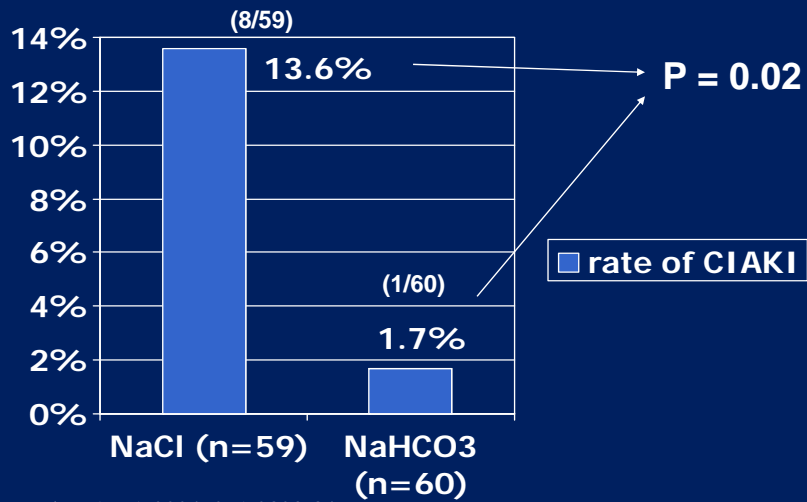
Questions to ask

- 1) Is pooling the results of underpowered, clinically heterogeneous studies in the presence of publication bias likely to permit meaningful summary estimates of NAC ??? NO
- 2) Is pooling the results of underpowered, clinically heterogeneous studies in the presence of publication bias likely to lead to confusion on the role of NAC and calls to conduct a definitive trial ??? YES

Impact of equipoise on NAC

- Use of NAC in 660 high-risk pts undergoing CE procedures:
 - 39% use overall
 - 84% use with coronary angiography
 - 17% use with CT scan
 - 12% use in lieu of IV fluids
- 87 providers who ordered CE procedures were surveyed on their knowledge of effectiveness of NAC to prevent CIAKI
 - 54% said effective
 - 24% said ineffective
 - 22% said not sure

NaHCO₃ vs. NaCl – initial clinical trial (N=129)



Merten et al – JAMA 2004; 291:2328-34

Clinical trials of bicarbonate (N=10)

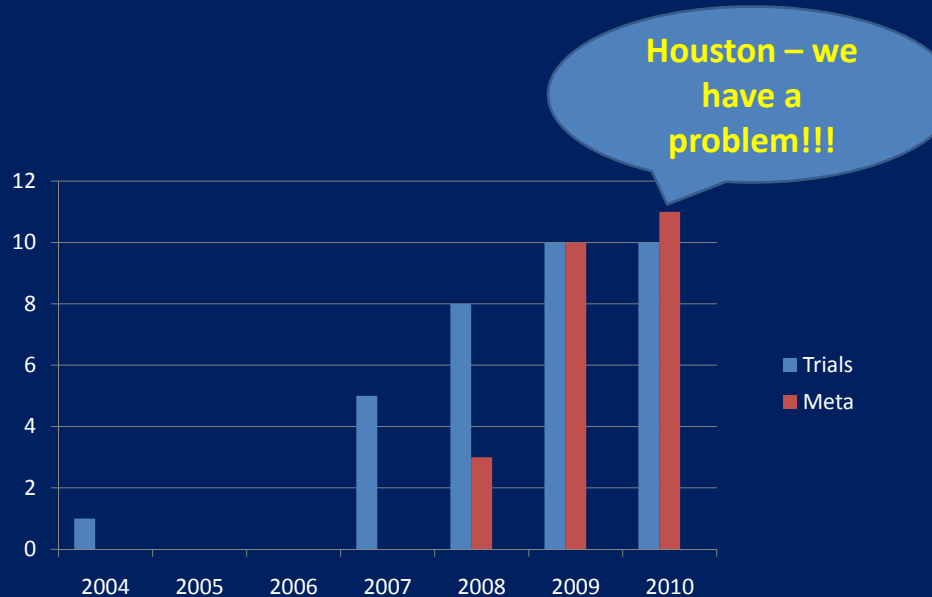
- Varying sample size - 59 to 502 pts
- Varying baseline SCr – 1.0 mg/dL to 2.0 mg/dL
- 5 different definitions of CIAKI
- Assumed fx size:
 - Not reported in 2 studies
 - ≥ 50% in all 8 other studies

Intra-trial heterogeneity in IV fluids

- 2 trials, including largest to date, used different regimens for NaCl and NaHCO₃
 - NaCl - 1 ml/kg/hr x 12 hrs pre and post
 - NaHCO₃ – 3 ml/kg/hr x 1 hr pre and 1 ml/kg/hr x 6 hr post

Maoli et al. JACC 2008;52:599-604

publications of trials and meta analyses



Meta-analyses of bicarb

Positive fx

- Navaneethan et al. (n=12)
- Kanbay et al. (n=17)
- Brown et al. (n=10)*
- Ho et al. (n=4)
- Hogan et al. (n=7)
- Joannidis (n=9)
- Meier et al. (n=17)
- Kunadian (n=7)

Negative/inconclusive fx

- Zoungas et al. (n=23)
- Brar et al. (n=15)
- Hoste et al. (n=18)

Methodological issues with primary trials & pooling results

- Enormous clinical heterogeneity
 - Pt populations, procedures, dose and duration of IV fluids, co-interventions
- Inclusion of lower risk pts
 - nl SCr, non-diabetics
- Small sample size based on implausible fx sizes

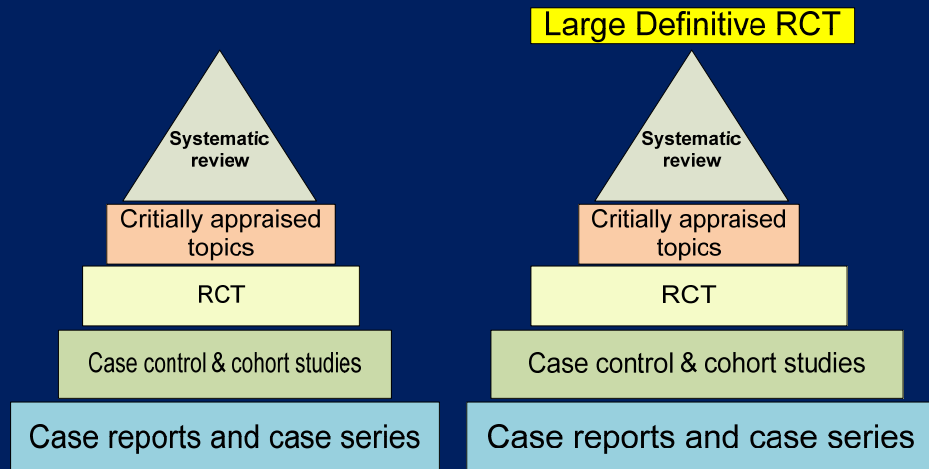
Statistical heterogeneity in meta-analyses of bicarbonate

- 10/11 meta-analyses reported heterogeneity
- 1/11 meta-analysis reported no heterogeneity
 - study contained 4 clinical trials
- 2 studies concluded that b/c of heterogeneity, no conclusions could be drawn

Publication bias

- 9/11 studies reported presence of pub. bias
- 2/11 did not report pub. bias

Which pyramid applies with bicarb?



9/11 studies concluded that large, randomized trials are needed to clarify the benefit of bicarbonate

Impact of equipoise on bicarbonate

- Use of IV fluids in 660 high-risk pts undergoing CE procedures:
 - 43% received pre-procedure IVF
 - 13% NaCl, 23% NaHCO₃, 7% hypotonic NaCl
 - 48% received post-procedure IVF
 - 13% NaCl, 17% NaHCO₃, 18% hypotonic fluids
- 1) Overall there is under-utilization of IVF
 - 2) Highly variable use of IVF

Impact of equipoise on bicarbonate

- Survey of 87 providers ordering CE procedures asked if NaHCO₃ is effective for the prevention of CIAKI:
 - 54 % yes
 - 20% no
 - 28% don't know

Conclusion

- CIAKI is common and associated with adverse outcomes
- Preventive role of NAC and NaHCO₃ not determined by multiple, small, underpowered trials
- There are no short cuts to determining the role of these 2 interventions
- The most important conclusion of these meta-analyses is that a large, well powered clinical trial is in fact, needed