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Kontrast ved nyreinsufficiens

Hovedsynspunkter

- Kontrastforstærkede undersøgelser skal kun benyttes, når det er nødvendigt
  - Kan vi få den ønskede information ved kontrastfri undersøgelse evt med anden modalitet ?
- Jod- og Gd-holdig kontrast kan godt benyttes ved nyresygdom
  - Klar og tungtvejende indikation
  - Omtanke – kontrasttype, dosering, forholdsregler

Kontrast-nefropati
CIN – contrast-induced nephropathy
CI-AKI – contrast-induced acute kidney injury

Mekanisme

- Agens
  - Jod-holdig røntgenkontrast
    - Arteriel vs venøs, høj- versus iso/lavosmolær
  - Gd-holdig MR-kontrast
- Patofysiologi
  - Direkte tubulus-toxicitet
  - Hæmodynamisk effekt – øget blodviskositet?
- ATN – akut tubulær nekrose
  - Oftest reversibel

Forløb

- Max nyrepåvirkning dag 3-5 efter exp
- Remission over 1-3 uger
- Sjældent varig skade

Definition og hyppighed

Mehran & Nikolsky, KI 2006;69:S11-S15

- CIN-def
  - Kontrast-exposition efterfulgt af kreatinin-stigning på 25% eller 44 uM inden for 2-3 døgn
- Incidens: 0.6-2.3%
  - I risikogrupper op til 50%
- Incidens af dialysebehov: < 1‰
  - Incidens i risikogrupper 3‰
    - ACT, Circulation 2011

Table 1 | Risk factors for the development of CIN

Fixed (non-modifiable) risk factors	Modifiable risk factors
Older age	Volume of CM
Diabetes mellitus	Hypotension
Pre-existing renal failure	...ia and blood loss
Advanced CHF	Dehydration
Low LVEF	Low serum albumin level (<35 g/l)
Acute myocardial infarction	...bitors
Cardiogenic shock	Diuretics
Renal transplant	Non-steroidal anti-inflammatory drugs
	Nephrotoxic antibiotics
	IABP

Inc: 5-30%

Inc: 10-55%

Inc: 3-20%

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CIN, contrast-induced nephropathy; CM, contrast media; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction.

Mehran & Nikolsky, KI 2006;69:S11-S15

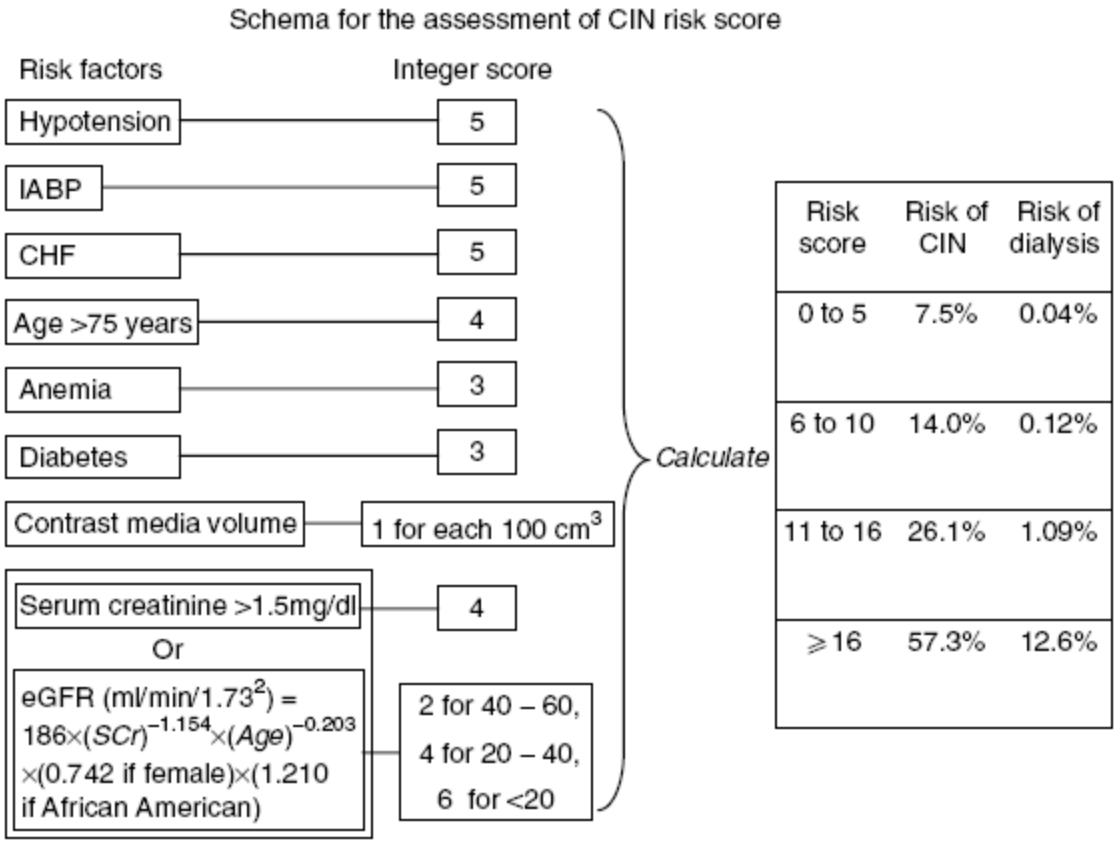


Figure 3 | Scheme to define CIN risk score. CHF denotes congestive heart failure class III–IV by the New York Heart Association classification and/or history of pulmonary edema. eGFR denotes estimated glomerular filtration rate by Modification of Diet in Renal Disease formula. Anemia: baseline hematocrit value <39% for men and <36% for women. Hypotension: systolic blood pressure <80 mm Hg for at least 1 h requiring inotropic support with medications or IABP within 24 h periprocedurally.

Mehran & Nikolsky KI 2006

CIN – kan det forebygges?

- JA
  - Kontrasttype og - mængde
  - Korriger modificerbare risikofaktorer
    - Hydrering (KDIGO, KI 2012;2:S69-S88)
      - Saltvand/Na-bikarbonat isot
      - Start min 1 timer før, fortsæt min 3 timer efter
      - Min 1 ml/kg/t
      - Praksis: Fx 200 ml/t i 2 timer før, 100 ml/t i 6 timer efter – i alt 1 L
    - Medikamenter
      - NSAID, genta, diuretika, ACEI/AT2A pauseres døgnet før
    - Anæmi

CIN-forebyggelse med acetylcystein??

- Sensationel nyhed i 2000
  - Martin Tepel – i dag prof i nefrologi, OUH
    - NEJM 2000;343:180-184
  - Hypotese
    - Kontrast giver oxidativ skade og dermed CIN
    - Acetylcystein har antioxidant virkning – ingen CIN?
  - Design
    - Randomiseret, ublindet
    - n = 83 CKD patienter, krea > 106 uM, middel 216 uM
    - +/- 600 mg acetylcystein x 2 i 2 døgn

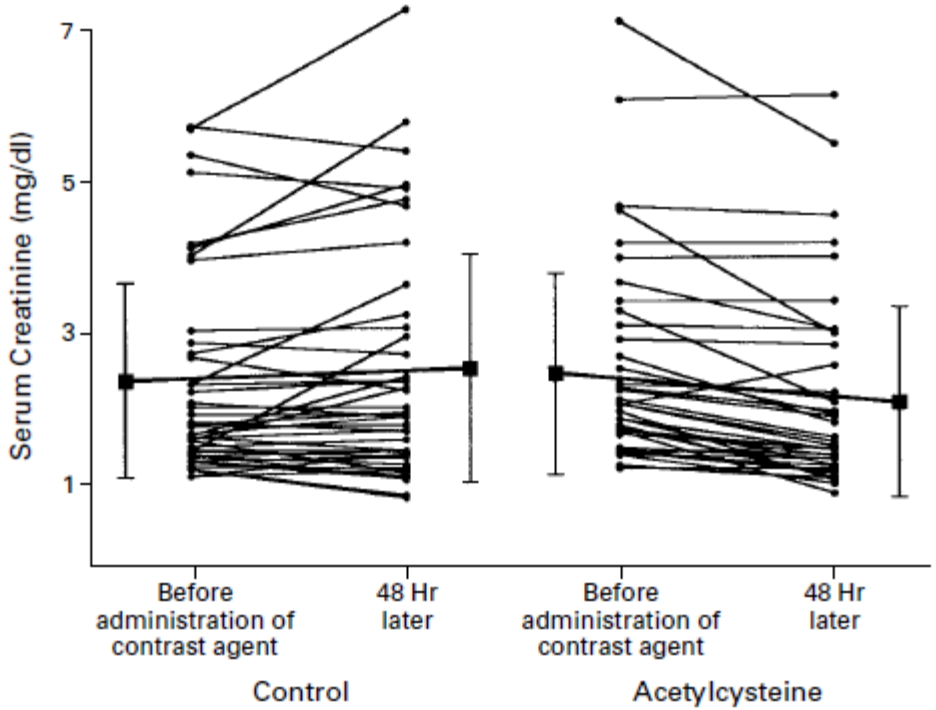


Figure 1. Serum Creatinine Concentrations before and 48 Hours after the Administration of Contrast Agent to Patients with Chronic Renal Insufficiency.

Mean (±SD) concentrations for the acetylcysteine group (41 patients) and for the control group (42 patients) are indicated by squares and vertical lines. To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

Resultater

Tepel – NEJM 2000

- CIN (+44 uM over 48 t) incidens
  - Aktiv: 1 af 41 – 2%
  - Placebo: 9 af 42 – 21%
  - Højsignifikant forskel
- Men…
  - Lille og ublindet studie
  - Ingen sign krea-stigning i kontrolgruppen
  - Og sign fald i krea i aktiv-gruppen???

Siden Tepel

- Mange små, non-lege-artis udførte studier
  - Inkonsistente fund
- Næsten lige så mange systematiske reviews
  - Inkonsistente konklusioner
- KDIGO konsensus konklusion 2012 (KI 2012; suppl 2)
  - "the overall benefit is not consistent or overwhelming"
  - "we suggest using oral NAC in patients at risk of CI-AKI"
- Men så kom ACT
  - Circulation 2011;124:1250-59

ACT

Circulation 2011; 124: 1250-59

- Brasiliansk (!) multicenter studie
  - Randomiseret, dobbeltblindet, intention-to-treat
  - n = 2308 med min 1 risikofaktor for CI-AKI og henvist til angiografi (67% KAG, 29% PCI)
  - +/- NAC 1200 mg x 2 i 2 døgn
    - Alle : Isot saltvand, 1 ml/kg/t, min -6 til +6 t
  - Blodprøver: Baseline, +48-96 t og +30 d efter exp
  - Primær effekt: +25% krea-stigning
  - Sekundære effekter: Dialysebehov, død m.v

ACT

Circulation 2011; 124: 1250-59

Table 1. Baseline Characteristics of Patients

Characteristic	Acetylcysteine (n=1172)	Placebo (n=1136)
Female sex, No. (%)	445 (38.0)	447 (39.3)
Age, mean±SD, y	68.0±10.4	68.1±10.4
Patients fulfilling inclusion criteria		
Serum creatinine >132.6 μmol/L (1.5 mg/dL), No. (%)		
Diabetes mellitus, No. (%)		
Known heart failure, No. (%)		
Hypotension, No. (%)		
Age >70 y, No. (%)		
Acute coronary syndrome, No. (%)	419 (35.8)	397 (34.9)
History of hypertension, No. (%)	1,014 (86.5)	976 (85.9)
Previous medication		
Use of NSAIDs >7 d, No. (%)	63 (5.4)	59 (5.2)
Use of ACE inhibitor, No. (%)	698 (59.6)	661 (58.2)
Use of diuretics, No. (%)	442 (37.7)	401 (35.3)
Use of metformin, No. (%)	362 (30.9)	336 (29.6)
Serum creatinine, mg/dL	1.2±0.5	1.2±0.5
Estimated creatinine clearance, mL/min*		
Mean±SD	67.6±31.4	67.7±32.1
<30 mL/min, No. (%)		
30 to 60 mL/min, No. (%)	515 (43.9)	492 (43.3)
>60 mL/min, No. (%)	589 (50.3)	581 (51.2)

16% med krea > 133 uM

60% diabetikere

52% over 70 år

6% med eGFR < 30 ml/min

Table 3. End Points

Outcomes	Acetylcysteine	Placebo	Relative Risk (95% CI)	*P*
Primary end point, No. of events/total No. (%)				
Contrast-induced acute kidney injury	147/1153 (12.7)	142/1119 (12.7)	1.00 (0.81–1.25)	0.97
Other end points, No. of events/total No. (%)				
End points in 48 to 96 h				
Doubling in serum creatinine	13/1153 (1.1)	17/1119 (1.5)	0.74 (0.36–1.52)	0.41
Elevation ≥44.2 μmol/L (0.5 mg/dL) in serum creatinine	45/1153 (3.9)	42/1119 (3.8)	1.04 (0.69–1.57)	0.85
Elevation ≥13.3 μmol/L (0.3 mg/dL) in serum creatinine	140/1153 (12.1)	123/1119 (11.0)	1.10 (0.88–1.39)	0.39
End points at 30 d				
Deaths or need for dialysis*	26/1171 (2.2)	26/1135 (2.3)	0.97 (0.56–1.69)	0.92
Death, need for dialysis, or doubling in serum creatinine	38/1171 (3.2)	41/1135 (3.6)	0.90 (0.58–1.39)	0.63
Deaths*	23/1171 (2.0)	24/1135 (2.1)	0.97 (0.54–1.73)	0.92
Need for dialysis*	3/1171 (0.3)	3/1135 (0.3)	0.87 (0.17–4.35)	0.86
Cardiovascular deaths*	18/1171 (1.5)	18/1135 (1.6)	0.99 (0.51–1.90)	0.97

CI indicates confidence interval.

*Results are hazard ratios with 95% CI and *P* values obtained by Cox regression.

CIN ved avanceret nyreinsufficiens

ACT Circulation 2011

- Subgruppe med eGFR < 30 ml/min
  - Aktiv 6/56
  - Placebo 3/48
  - RR hvis NAC: 1.71 (0.45-6.49)

ACT - konklusioner

Circulation 2011; 124: 1250-59

"In this large randomized trial, we found that acetylcysteine does not reduce the risk of contrast-induced acute kidney injury or other clinically relevant outcomes in at-risk patients undergoing coronary and peripheral vascular angiography"

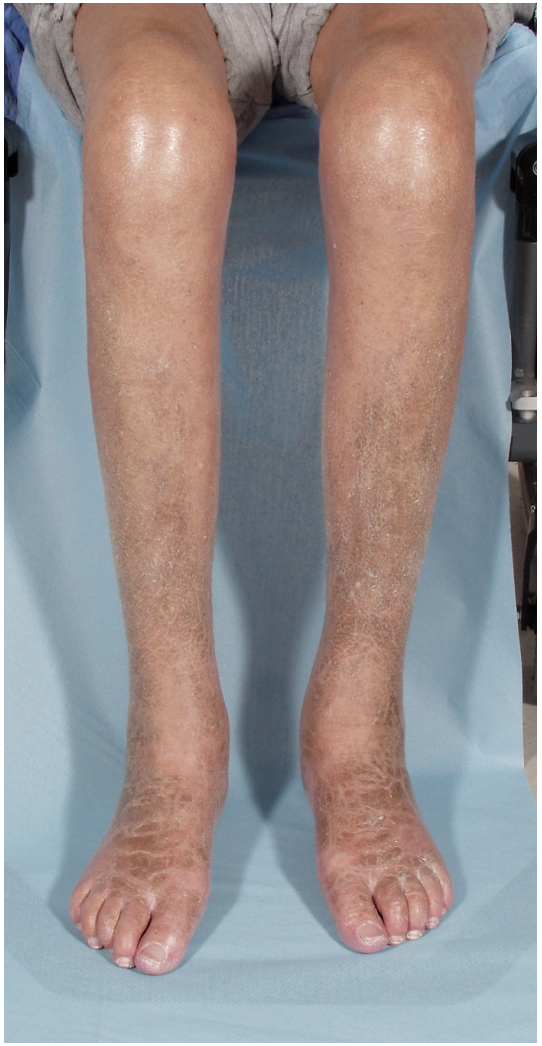
CIN – mine konklusioner

- Kontrastforstærket CT (eller MR) kan gennemføres trods CIN-risiko hvis stærk indikation
- I givet fald CIN-profylakse med
  - Hydrering efter bogen√
  - Medicinsanering √
  - Optransfundering √
  - Selekteret kontraststof √
  - - og opfølgende kreatinin-måling efter 2-3 døgn
- NAC – nytteløs (ligesom hæmodialyse)
- I overensstemmelse med ESUR guidelines

- og hvad så med metformin?

- eGFR > 45 ml/min: Ingen problemer
- eGFR < 45 ml/min:
  - Pauseres 48 timer før
  - Genoptages først når betydende kontrastnefropati er udelukket ved kreatinin-måling min. 48 timer efter

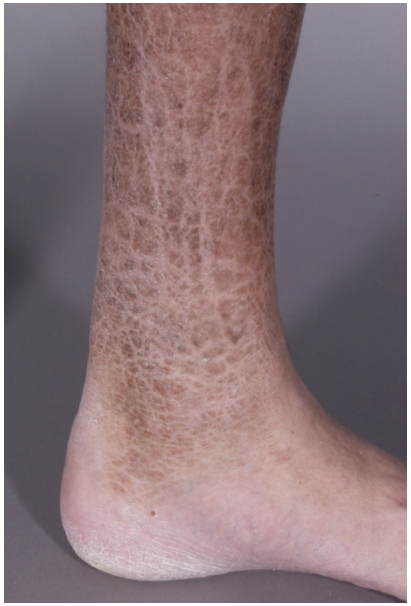
NSF - nefrogen systemisk fibrose

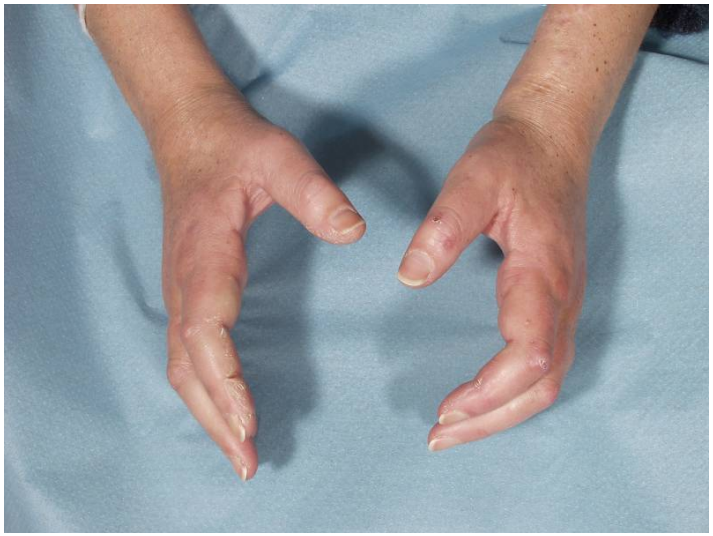


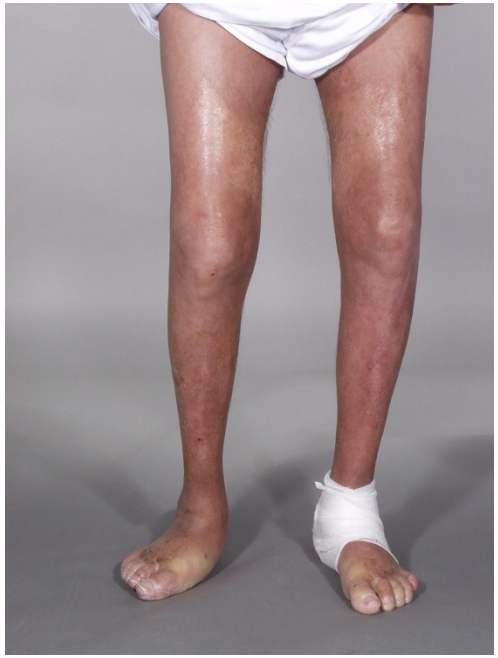
Woman, born 1971

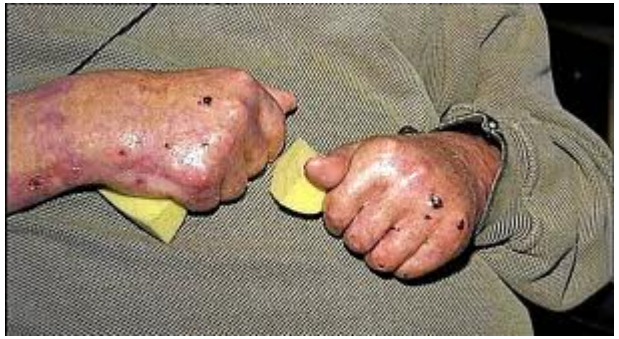
NSF from 2005

Died Jan 2008









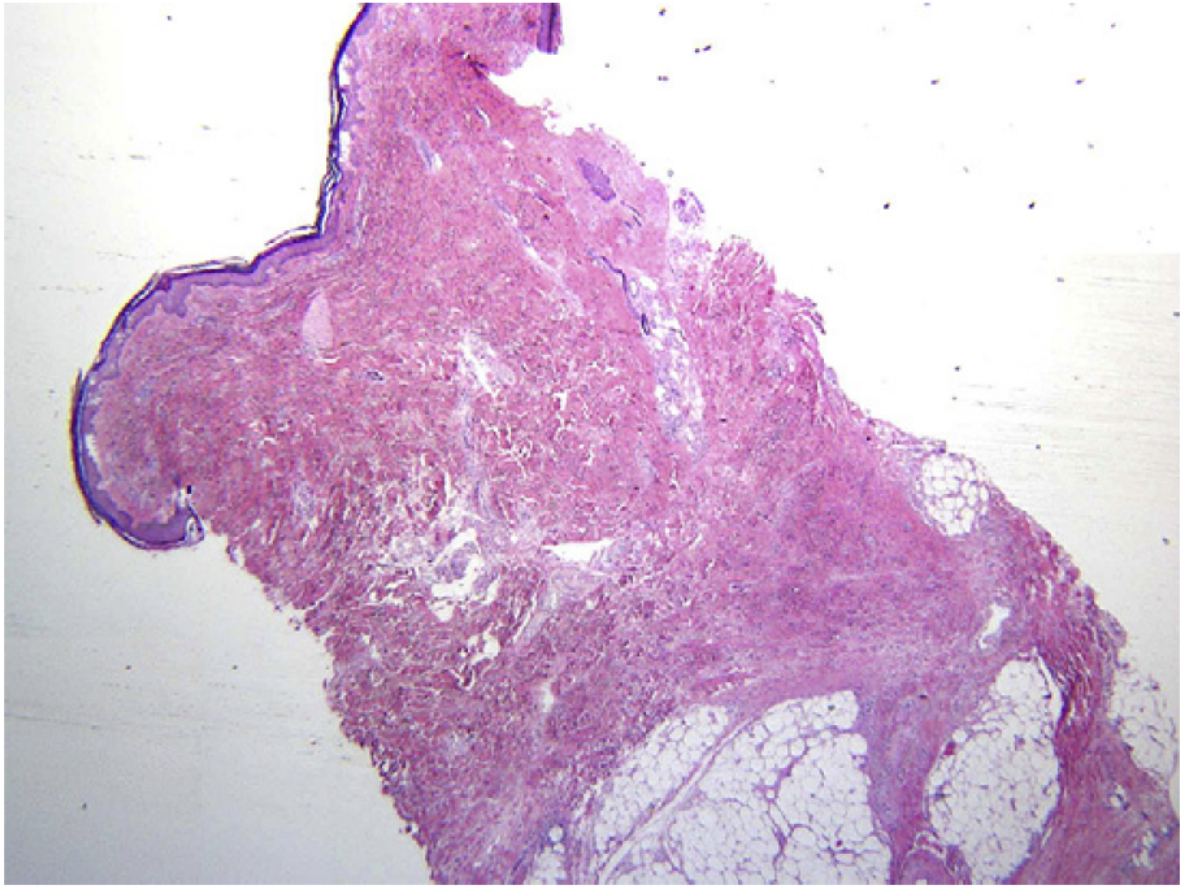
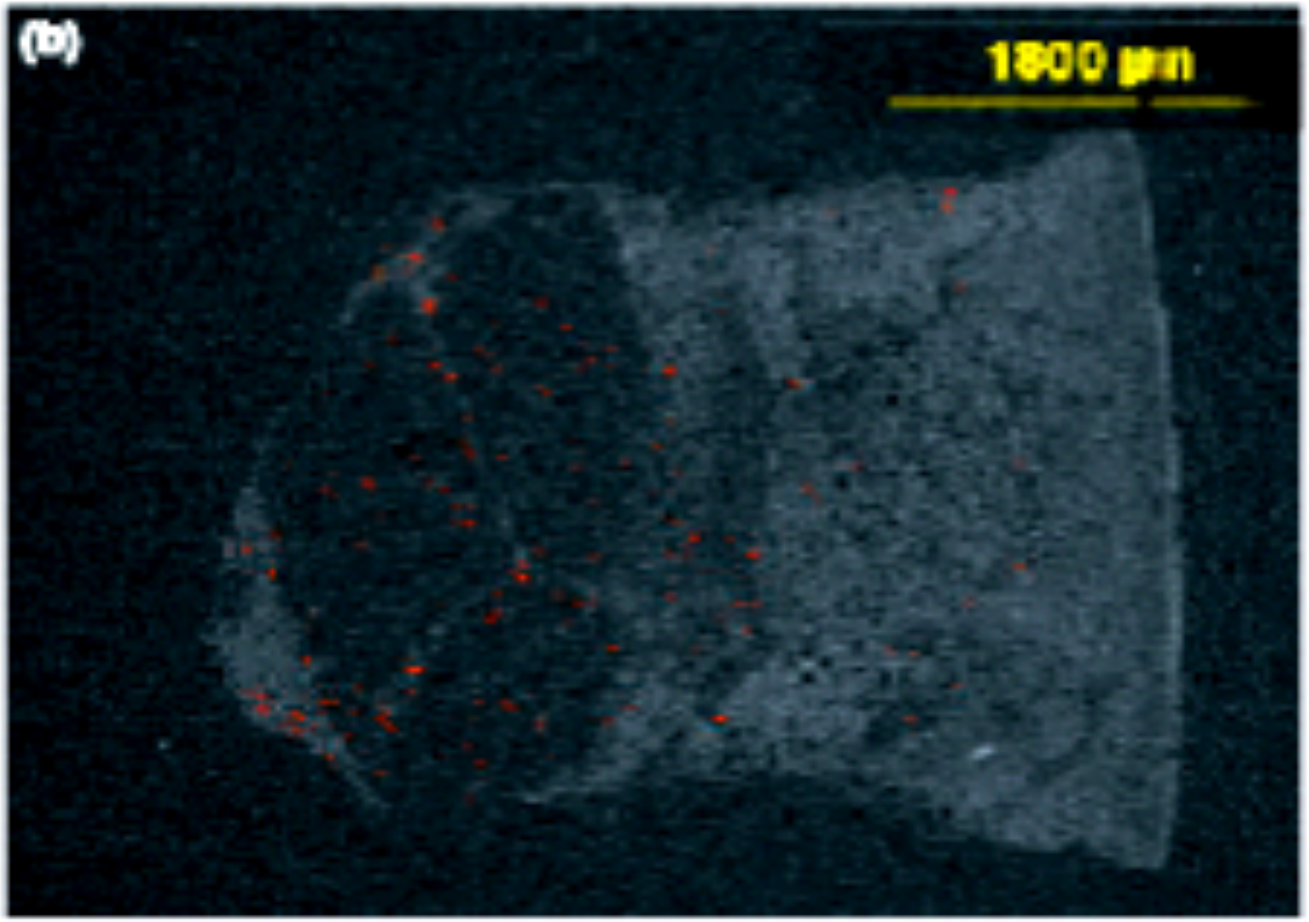


Fig. 1. NSF skin biopsy showing extension of the fibrotic process involving the subcutaneous septa between the lobules of adipose tissue.

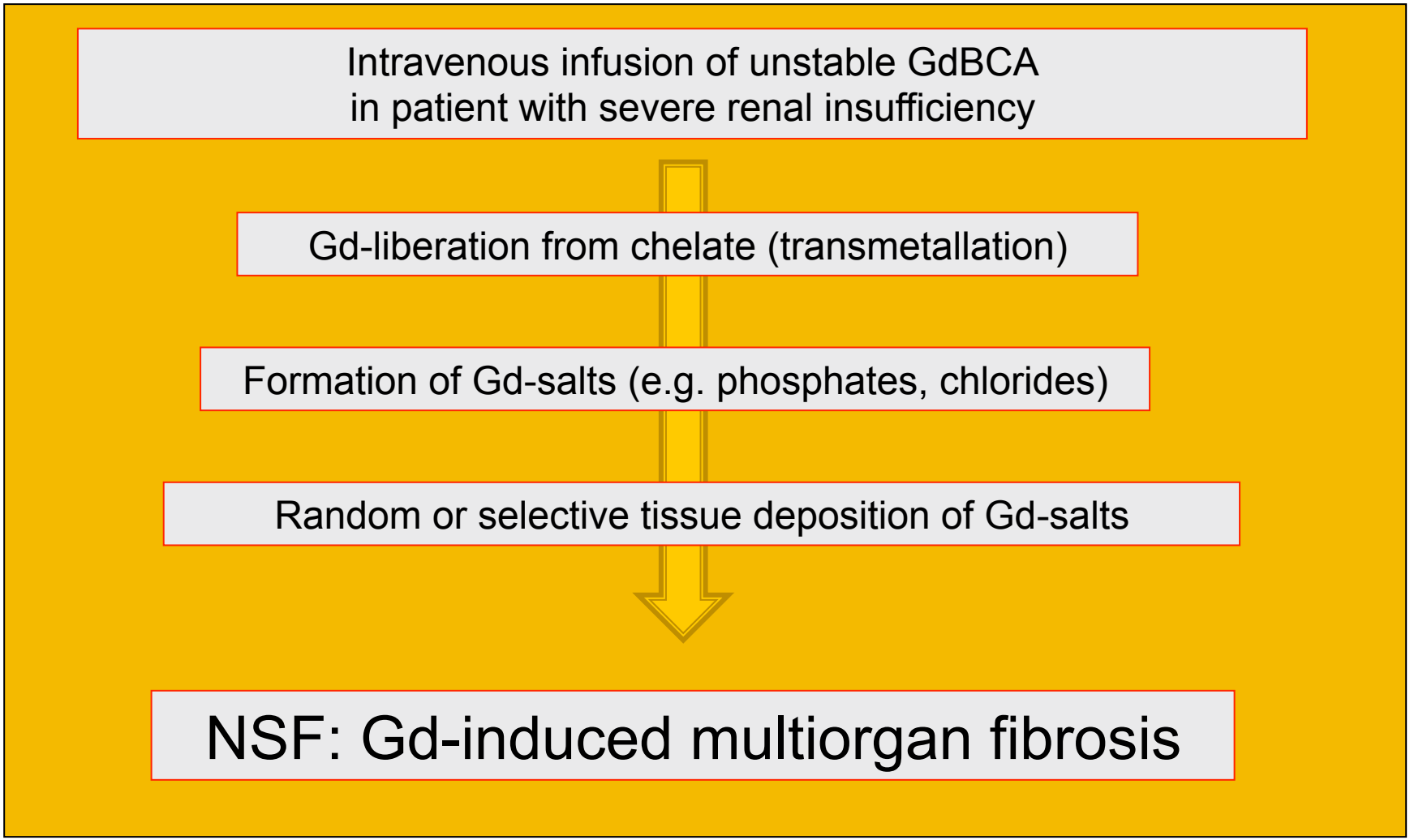
Thakral & Abraham Radiol Clin N Am 2009;47:841-853

Histochemical proof: inorganic Gd in NSF skin

Abraham et al, Brit J Dermatol 2008



NSF pathogenesis



Early phase of NSF – ”inflammation”

- Acute symptoms from extremities
  - Symmetric swelling, discoloration, increased warmth, severe itching, or pain
- Diffuse hair loss
- Acute abdominal symptoms
  - Diarrhoea, cramps, vomiting
- Acute lung symptoms
  - culture-negative bilateral lung infiltrates and hypoxia

Late phase of NSF – ”fibrosis”

- Fibrotic, hardened, hyperpigmented skin
  - Symmetric distribution
  - Primarily limbs, in particular ankles-to-knee region
  - Vary from minor elements to large, confluent areas
- Limited joint motion and contractures of affected regions
- Frequently also
  - Weakness, pain, itching, dysesthesia, numbness of extremities

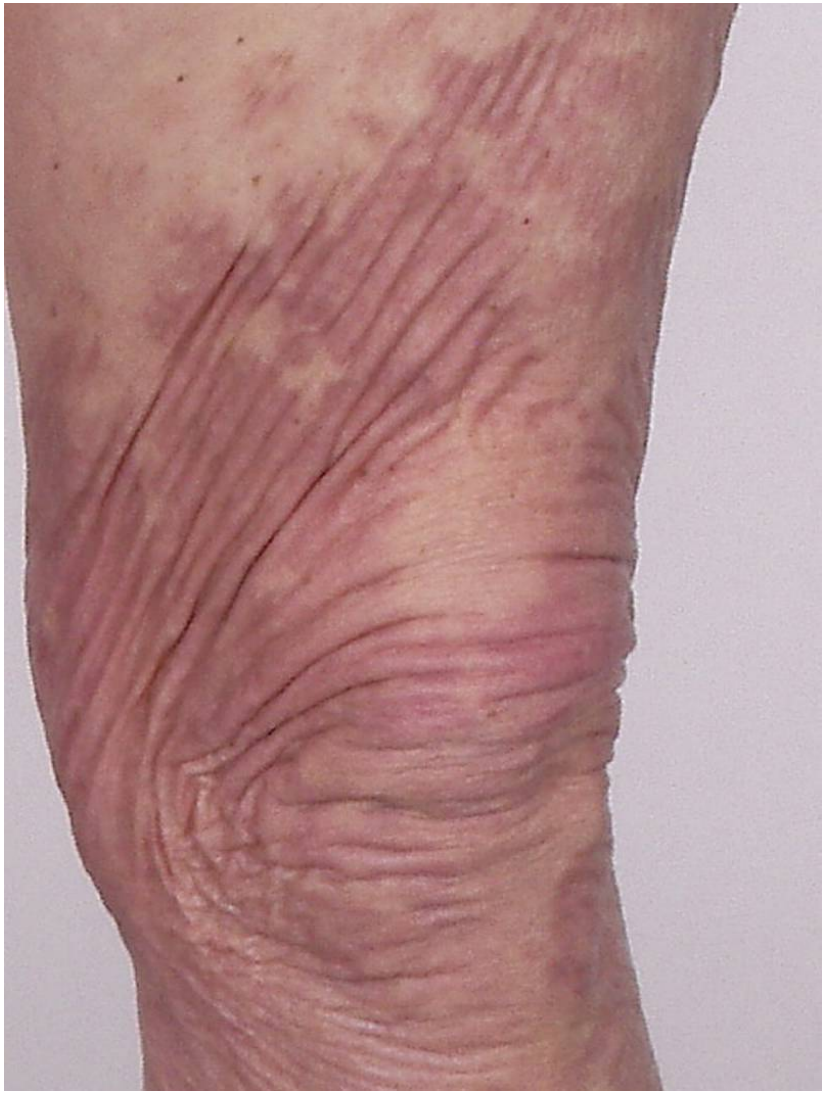
Diagnosing NSF

Marckmann et al, Clin Nephrol 2008, Marckmann & Skov, Radiol Clin N Am 2009

1. Relevant history including GdBCA
2. Characteristic clinical findings and patient complaints
3. Excluding differential diagnosis
    - Scleroderma, eosinophilic fasciitis, etc
4. Confirmative skin histology (deep skin biopsy)
5. Presence of Gd in skin biopsies

Caveats:

1. Skin histology may be unspecific (scar tissue)
2. GdBCA exposure may be undocumented
3. NSF patients may have atypical symptoms



NSF: How frequent?

- Rydahl, Invest Radiol 2008: Prevalence in cohort study
  - 18 NSF cases among 102 Omniscan CKD5 patients
    - 18% (95% CI: 11-27%)
  - 9 NSF among 27 CKD5 patients with repeated exposures
    - 33% (95% CI: 18-52%)
  - No cases among 88 exposed patients with GFR > 15 ml/min
    - 0% (95% CI: 0-4%)
- Others
  - Highly variable NSF prevalence after GdBCA: 0-55%
  - Explanations: population characteristics, completeness of case detection, dosing and type of GdBCA, others

NSF: How frequent?

Worldwide estimate:

DK + USA: 750 NSF cases

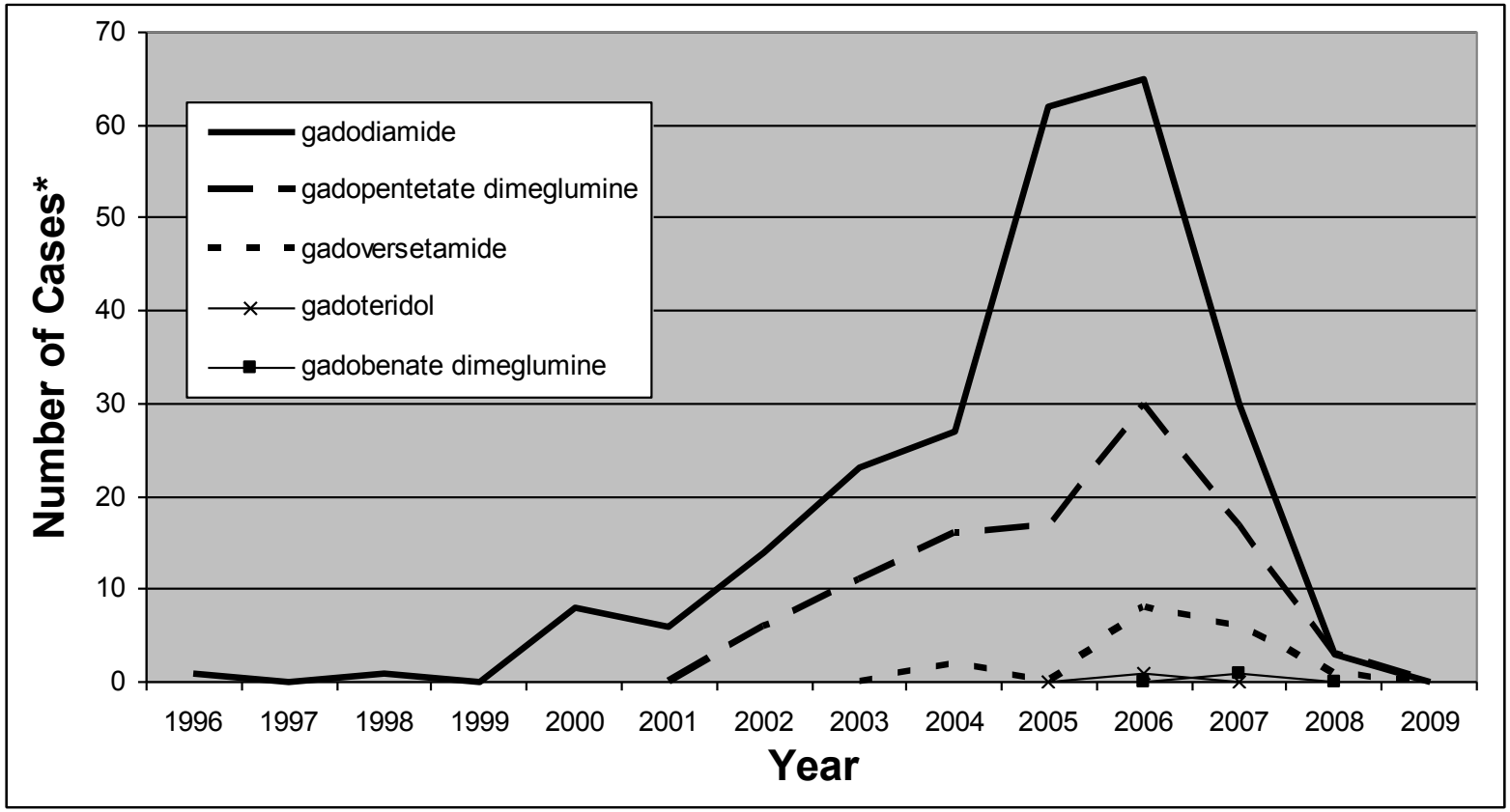
+ undiagnosed cases

+ undiagnosed, deceased cases

+ remaining world

2000-10000 NSF cases

FDA annual NSF-reports 1996-2009



GdBCA-kelaters karakteristika

Table 1: Generic Names, Trade Names, Physicochemical Characteristics and Scientifically Reported Cases of Nephrogenic Systemic Fibrosis of Nine Gd-based Contrast Agents

Generic Name	Trade Name	Chemical Structure	Ionicity	Thermodynamic Stability at pH 7.4	Kinetic Stability	NSF Cases
Gadodiamide	Omniscan	Linear	Non-ionic	Low	Low	+++
Gadoversetamide	OptiMark	Linear	Non-ionic	Low	Low	+++
Gadopentetate dimeglumine	Magnevist	Linear	Ionic	Medium	Low	++
Gadobenate dimeglumine	MultiHance	Linear	Ionic	High	Medium	–
Gadoxetic acid disodium	Primovist	Linear	Ionic	High	Medium	–
Gadofosveset trisodium	Vasovist	Linear	Ionic	High	Medium	–
Gadoteridol	ProHance	Macrocyclic	Non-ionic	Medium	High	–
Gadobutrol	Gadovist	Macrocyclic	Non-ionic	Low	High	+ (? – see text)
Gadoterate meglumine	Dotarem	Macrocyclic	Ionic	High	High	–

NSF = nephrogenic systemic fibrosis. In the column 'NSF cases' the number of + indicates the frequency of observed NSF cases relative to the number of patients exposed to the individual agent. Source: modified from Idee et al., 2009.[4]

Marckmann, US Nephrology 2011;6:40-44

GdBCA-retningslinjer SST 2013

	NSF-risiko	eGFR < 30 ml/ min	eGFR 30-59 ml/min	eGFR ≥ 60 ml/ min
Omniscan Magnevist Optimark	HØJ	Nix	Helst ikke	Helst ikke
MultiHance Primovist	MEDIUM	Tvingende indikation	Tvingende indikation	OK
Dotarem Gadovist ProHance	LAV	Tvingende indikation	OK	OK

Bemærk: GdBCA KAN bruges ved GFR < 30 ml/min

Hæmodialyse straks efter GdBCA til HD-patienter

Hovedsynspunkter, uændret:

- Kontrastforstærkede undersøgelser skal kun benyttes, når det er nødvendigt
  - Kan vi få den ønskede information ved kontrastfri undersøgelse evt med anden modalitet ?

- Jod- og Gd-holdig kontrast kan godt benyttes ved nyresygdom
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