Teaching Module V
Contrast-Induced Nephropathy – CIN
Contrast-Induced Nephropathy – CIN
This slide deck was prepared by

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NHS Trust
Contrast-induced nephrotoxicity (CIN)

Contents

- Pathophysiology
- Risk factors
- Clinical picture
- Incidence
- Outcome
- Prevention
  - Importance of the dose of CM
  - Areas of confusion
The kidney is the main route of elimination of CM

- Increase RVR
- Decrease GFR
- Diuresis
- Natriuresis
- Enzymurias
- Structural changes [Osmotic nephrosis]

Modulation of production of intrarenal vasoactive mediators

- ↑ Endothelin (vasoconstriction)
- ↑ Adenosine (vasoconstriction)
- ↓ NO (vasodilatation)
- ↓ Prostacycline (vasodilatation)

It represents the normal response of the kidney to CM exposure
CM → Normal kidneys, no risk factors → No clinical problem

Risk factors:
- Renal impairment + DM
- Dehydration
- Congestive heart failure
- Age over 70 years old
- Administration of nephrotoxic drugs
- Dose and type of CM
Contrast-media-induced nephrotoxicity (CIN)

Definition
It implies impairment in renal function: an increase in serum creatinine by more than 25% or 0.5 mg/dL has occurred within 3 days following the intravascular administration of contrast medium and the absence of alternative aetiology.
NEW definition

- CIN is a condition in which a decrease in renal function occurs within 3 days of the intravascular administration of CM in the absence of an alternative aetiology. An increase in serum creatinine by more than 25% or 44 µmol/l (0.5 mg/dl) indicates CIN.
Clinical picture of CIN

• The diagnosis is based on an increase in serum creatinine.

• Anuria may develop in severe cases.

• Dialysis is rarely required. (<1% of patients with CIN)
Incidence of CIN after IV administration

• Incidence of CIN is very low in patients with GFR >45ml/min (<1%)
• Incidence of CIN in patients with GFR <45ml/min varies between 5 - 20% (no studies in patient with eGFR <20ml/min)

• Sr Cr average 2.4 mg/dL 21% in the control arm (Tepel et al, New England Journal of Medicine 2000; 343: 180-184) – highest incidence ever reported.

Katzberg & Barrett, Radiology 2007; 243: 622-628
Combined data from a comparative study of a monomer and a dimer.

<table>
<thead>
<tr>
<th>eGFR (MDRD)</th>
<th>Relative risk of CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 ml/min</td>
<td>0.6%</td>
</tr>
<tr>
<td>&lt; 40 ml/min</td>
<td>4.6%</td>
</tr>
<tr>
<td>15 – 30 ml/min</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

Thomsen & Morcos Eur Radiol 2009; 19: 891-897
The Incidence increases as the renal function decreases

Estimate:
In patients with GFR < 20 ml/min is probably 10-15% after intravenous injection
The incidence is higher after intraarterial injection
Incidence of CIN in patients undergoing cardiac angiography (n=1,196)

Rudnick et al., 1995
DM increased the incidence of CIN in patients with renal impairment undergoing coronary angiography (n=1,826)

No CIN requiring dialysis was observed at CrCl of 50 ml or more

Incidence of CIN markedly increased at CrCl of 30 ml or less

100 ml was the cut-off dose of CM below which there was no CIN requiring dialysis

McCullough et al., Am J Med 1997; 103:368-375
The risk and severity of CIN increases proportionally to the number and severity of the risk factors.
CIN
Clinical course

Although self-limiting in most cases (resolve within 1-2 weeks)
Clinical importance of CIN

CIN increases the incidence of non-renal complications and prolongs hospital stay

Rihal et al., Circulation 2002; 105:2259-2265

Bartholemew et al., Am J Cardiol 2004; 93:1515-1519

Marenzi et al., JACC 2004; 44:1780-1785
Clinical importance of CIN
CIN increases in hospital mortality

- *21% - 34% in the CIN groups
  - *1%-7% in the control groups (similar baseline renal function, received CM without developing CIN)

- **CIN was significantly associated with 30-day mortality (15.6% with CIN Vv 5.2% control), the risk was higher after IV than after intraarterial administration!*

*Levy et al., JAMA 1996; 275:1489-149 (In this study, 48% of patients received IV CM)

**From AM et al., Mayo Clin Proc 2008; 83:1095-1100
CIN
PREVENTION IS CRUCIALLY IMPORTANT

To avoid an increase in patients’ morbidity and mortality

Levy et al., JAMA 1996; 275:1489-1494
How to reduce the risk of CIN
Prevention of CIN

• Small dose of low-osmolar or iso-osmolar non-ionic CM

• Volume expansion

• Prophylactic haemodialysis

• Haemofiltration

Can be considered in patients with advanced renal disease (Cr CI ≤ 30 ml/min) requiring interventional vascular procedure
Prevention of CIN
Pharmacological manipulation

Renal vasodilators
- Calcium channel blockers
- Dopamine
- Atrial natriuretic peptide
- Fenoldopam [dopamine-1 receptor agonist]
- Prostaglandin E1

Blocking intrarenal mediators
  [ET, Adenosine]
  - ET receptor antagonist
  - Theophylline

Cytoprotective drugs
- Acetylcysteine
- Acetazolamide

Value remains uncertain
Importance of dose in CIN

The higher the dose the higher the risk

The maximum dose of CM in gram iodine that can be given without significantly increasing the risk of CIN

Dose of CM in gram iodine should not exceed the value of eGFR

*The dose of CM should never exceed the amount required to produce essential diagnostic information*

Nyman et al., Acta Radiologica 2008; 49:658-667

ESUR guidelines book
How to reduce the dose of CM IA administration

- ICM + CO$_2$
- Reducing the iodine concentration
- Focus only on essential diagnostic information
Areas of confusion in prevention of CIN

• Identifying patients at risk
• Hydration regime
• The type of CM (IOCM or LOCM)
• The prophylactic use of acetylcysteine
Identifying patients with renal impairment

Serum Cr measured routinely before contrast injection

or

Selective measuring of Sr Cr using a questionnaire
(history of renal disease, proteinuria, prior kidney surgery, hypertension, gout or diabetes mellitus)

Morcos SK, Clin Radiol 2004; 59:381-389
Choyke et al., Techniques in Urology 1998; 2:65-69
Serum Creatinine can be used to calculate eGFR

eGFR < 45 ml/min is a risk factor for CIN after IV administration

eGFR < 60 ml/min is a risk factor for CIN after IA administration
Areas of confusion

Hydration

• Type of fluid
  • Half-strength saline
  • Normal saline
    or
  • Sodium bicarbonate

• Hydration regime
  • Orally
  • IV
  • Duration
Hydration

Goals

- Diuresis
  - Dilute CM in the tubules
  - Decrease contact time
  - Increase production of prostacycline in renal medulla
  - Suppress TGF response

- Volume expansion
  - Suppress renine-angiotensine system
  - Suppress ADH

- $\text{HCO}_3$
  - Increase pH of urine and renal medulla
  - Suppress production of free radicals
The type of fluid

• A study by Mueller et al. demonstrated that 0.9% saline is superior to 0.45% preparation in reducing the risk of CIN in patients undergoing coronary angioplasty
  
  Mueller et al., Arch Intern Med 2002; 162:329-336

• A recent study of 353 patients undergoing coronary angiography (MEENA trial) showed no benefit of sodium bicarbonate over normal saline in preventing CIN
  
  Brar et al., JAMA 2008; 300:1038-46
Hydration with sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of randomized controlled trials

H. Trivedi¹, R. Nadella¹ and A. Szabo²

¹Division of Nephrology and ²Department of Population Health, Medical College of Wisconsin, Milwaukee, WI, USA

Abstract. Background: Whether hydration with sodium bicarbonate is beneficial for the prevention of contrast-induced nephropathy is uncertain. Methods: We conducted a meta-analysis of trials to evaluate the benefit of sodium bicarbonate solutions for the prevention of contrast-induced nephropathy. Our pre-specified criteria were: 1) adult subjects; 2) English literature; 3) randomized trials of individuals assigned to a bicarbonate-containing intravenous fluid, is a major cause of morbidity and mortality. It is the third leading cause of hospital-acquired acute kidney injury [1]. There is no treatment of established disease other than management of fluid and electrolyte disturbances as in acute kidney injury of any etiology. Hence the focus has been on preventive measures. However, therapy to prevent contrast-induced nephropathy is still a challenge.
Conclusion:

Though inference should be tempered by trial quality issues, given lack of heterogeneity or publication bias the summary effect of randomized trials balanced in important characteristics favors hydration with sodium bicarbonate for the prevention of contrast-induced nephropathy.
### Incidence of CIN

<table>
<thead>
<tr>
<th>Study</th>
<th>Total N</th>
<th>Sodium Chloride^</th>
<th>Sodium Bicarb^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merten (2004)</td>
<td>119</td>
<td>13.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Chen (2007)</td>
<td>105</td>
<td>14.0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Heguilen (2007)</td>
<td>18</td>
<td>11.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Kim (2007)</td>
<td>49</td>
<td>12.5%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Kim (2007)</td>
<td>51</td>
<td>25.0%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Lin (2007)</td>
<td>45</td>
<td>25.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Masuda (2007)</td>
<td>59</td>
<td>34.5%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Ozcan (2007)</td>
<td>176</td>
<td>13.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Adolph (2008)</td>
<td>145</td>
<td>2.7%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Brar (2008)</td>
<td>323</td>
<td>16.4%</td>
<td>15.8%</td>
</tr>
</tbody>
</table>
New recommendation from ESUR

- Sodium bicarbonate seems to provide equal or superior protection against CIN to normal saline.
- Current recommendations
  - Dose of N saline: 1.0-1.5 ml/kg/h for at least 6 hours before and after CM administration.
  - Dose of sodium bicarbonate: 3ml/kg/h for 1 hour before contrast medium followed by 1 ml/kg/h for 6 hours after – increase dose until urine alkanisation is achieved.
• **Oral hydration** (1000 ml over 6-8 h before and 1000 ml over 6-8 h after contrast exposure) could be adequate for patients with
  
  • eGFR between 30 to 45 ml/min
  
  • Receiving IV ≤ 100 ml of CM
  
  • If the dose of CM ≥ 100 ml, consider IV hydration
Hydration

100 ml/hr of normal saline IV for 4-6 hours before and after CM injection in addition to encouraging oral fluid intake

• IA administration of CM
  • eGFR < 60 ml/min

• IV injection of CM
  • > 100 ml + renal impairment
    (eGFR 30 to 45 ml/min)
    or
  • eGFR < 30 ml/min
Type of CM

Are iso-osmolar CM less nephrotoxic in comparison to LOCM after IV administration?
Based on 25 trials

Iodixanol is not associated with a significantly reduced risk of CIN compared with the LOCM pooled together.

However, in patients with intraarterial administration and renal insufficiency, iodixanol is associated with a reduced risk of CIN compared with iohexol, whereas no significant difference between iodixanol and other LOCM could be found.

Heinrich et al., Radiology 2009; 250:68-86
IOCM Vv LOCM angiography, diabetic patients with renal impairment

Comparing Iodixanol Vv Iopamidol in coronary angiography

• Incidence of CIN
  • Iopamidol 9.8%
  • Iodixanol 11.2%

No significant difference in the risk of CIN between iopamidol and iodixanol

Laskey et al. (Nephric 2), Am Heart J 2009; 158:822-823
CIN Comparative Studies after IV Injection
High risk patients (20-60 ml/min)

<table>
<thead>
<tr>
<th>Study</th>
<th>LOCM concentrate used</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraro et al (1998)</td>
<td>Iodixanol</td>
<td>0/32</td>
</tr>
<tr>
<td>Nguyen et al 2008</td>
<td>Iopromide</td>
<td>1/32</td>
</tr>
<tr>
<td>Barrett et al (2006)</td>
<td>Iopamidol</td>
<td>0/77</td>
</tr>
<tr>
<td>Thomsen et al (2008)</td>
<td>Iomeron</td>
<td>0/76</td>
</tr>
<tr>
<td>F-R Chuang (2009)</td>
<td>Iohexol</td>
<td>1/25</td>
</tr>
</tbody>
</table>

Patients with pre-existing renal impairment are at risk of CIN with all classes of CM

Morcos SK, Clin Rad 2009

TOTAL

(5.18%)  (5.26%)  NO DIFFERENCE
Acetylcysteine

• Low cost
• Ease of administration
• Limited side-effects
Acetylcysteine
Pharmacology

• Low oral bioavailability (6-10%)

• Other substances used in the oral formulation or administered concomitantly may combine with the sulfhydryl group, which is the key to its mechanism of action

Shalansky et al., Heart 2005; 91:997-999
Acetylcysteine
Disadvantages

- Optimal dosage remains uncertain (600 mg b.d or 1200 mg b.d for 48 hr)
- Activity varies between oral products
- Noxious smell and taste of liquid preparations
- Exact mechanism to prevent CIN is unknown
- Induces creatininuria leading to a reduction in serum creatinine independent of a change in GFR
Acetylcysteine

• Results of clinical studies are remarkably inconsistent

• Many uncertainties remain concerning its effectiveness
Acetylcysteine & IOCM

The conclusion of the first author of the Nephric study (Aspelin) and the author of the first paper on acetylcysteine (Tepel) in a recent review

• “Low-osmolar or iso-osmolar contrast media should be used to prevent CIN”

• “There is limited evidence that any pharmacological intervention, e.g. acetylcysteine, may prevent CIN”

Tepel M, Aspelin P, Lameire N, Circulation 2006; 113:1799-1806
CONTRAST MEDIA NEPHROTOXICITY
ESUR GUIDELINES

Risk factors

Look for:

• High serum creatinine levels, particularly secondary to diabetic nephropathy

• Dehydration

• Congestive heart failure

• Age over 70 years old

• Concurrent administration of nephrotoxic drugs, e.g. non-steroidal anti-inflammatory drugs
CONTRAST MEDIA NEPHROTOXICITY
ESUR GUIDELINES

In patients with risk factor(s)

Do:

• Make sure that the patient is well hydrated

• Use non-ionic contrast media

• Stop administration of nephrotoxic drugs for at least 24 h

• Consider alternative imaging techniques which do not require the administration of iodinated contrast media
CONTRAST MEDIA NEPHROTOXICITY
ESUR GUIDELINES

In patients with risk factor(s)

Do not:

• Give high-osmolality contrast media

• Administer large doses of contrast media

• Administer mannitol and diuretics, particularly loop diuretics

• Perform multiple studies with contrast media within a short period
### 2.1 Renal adverse reactions to iodinated contrast media

<table>
<thead>
<tr>
<th>Risk factors for contrast medium induced nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient related</strong></td>
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<tr>
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<td></td>
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<tr>
<td><strong>Procedure-related</strong></td>
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<td></td>
</tr>
</tbody>
</table>

Department of Diagnostic Sciences, CPH University
# 2.1.1. Time of referral

## Elective Examination

<table>
<thead>
<tr>
<th>1) Identify patients with eGFR less than 60 ml/min/1.73m² (or raised serum creatinine)</th>
<th>Determine eGFR within 7 days of contrast medium administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients with known eGFR less than 60 ml/min/1.73m²</td>
<td></td>
</tr>
<tr>
<td>• Diabetic patients taking metformin</td>
<td></td>
</tr>
<tr>
<td>• Patients who will receive intra-arterial contrast medium</td>
<td></td>
</tr>
<tr>
<td>• Patients who have a history suggesting the possibility of reduced GFR:</td>
<td></td>
</tr>
<tr>
<td>o Renal disease</td>
<td></td>
</tr>
<tr>
<td>o Renal surgery</td>
<td></td>
</tr>
<tr>
<td>o Proteinuria</td>
<td></td>
</tr>
<tr>
<td>o Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>o Hypertension</td>
<td></td>
</tr>
<tr>
<td>o Gout</td>
<td></td>
</tr>
<tr>
<td>o Recent nephrotoxic drugs</td>
<td></td>
</tr>
</tbody>
</table>
2.1.1. Time of referral

1. Identify **at risk** patients if possible:
2. Determine eGFR if the procedure can be deferred until the result is available without harm to the patients
3. If eGFR cannot be obtained, follow the protocols for patients with eGFR less than 60/ml/min/1.73 m$^2$ for intraarterial administration and eGFR less than 45 ml/min/1.73 m$^2$ for intravenous administration as closely as clinical circumstances.
### 2.1.2. Before the examination

#### Elective Examination

| **At risk patients** | • Consider an alternative imaging method not using iodinated contrast media.  
|                      | • Discuss the need to stop nephrotoxic drugs with the referring physician.  
|                      | • Start volume expansion. A suitable protocol is intravenous saline, 1.0-1.5 ml/kg/h, for at least 6 h before and after contrast medium. An alternative protocol is intravenous sodium bicarbonate, 3ml/kg/h for 1 h before contrast medium and 1 ml/kg/h for 6 h after contrast medium. |

Department of Diagnostic Sciences, CPH University
### 2.1.2. Before the examination

**Emergency Examination**

| At risk patients | • Consider an alternative imaging method not using iodinated contrast media.  
|                  | • Start volume expansion as early as possible before contrast medium administration. |

Department of Diagnostic Sciences, CPH University
### 2.1.3 Time of examination

| At risk patients | Use low or iso-osmolar contrast media  
<table>
<thead>
<tr>
<th></th>
<th>Use the lowest dose of contrast medium consistent with a diagnostic result.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not at increased risk</td>
<td>Use the lowest dose of contrast medium consistent with a diagnostic result.</td>
</tr>
</tbody>
</table>
2.1.3 Time of examination

| At risk patients                                      | • Use low or iso-osmolar contrast media          |
|                                                      | • Use the lowest dose of contrast medium consistent with a diagnostic result. |
| Patients not at risk                                  | • Use the lowest dose of contrast medium consistent with a diagnostic result. |
2.1.4. After the examination

| At risk patients | Continue volume expansion  
|                  | Determine eGFR 48-72 h after contrast medium. |
• No pharmacological manipulation (with renal vasodilators, receptor antagonists of endogenous vasoactive mediators or cytoprotective drugs) has yet been shown to offer consistent protection against contrast medium induced nephropathy.
Thank you for your attention