Chlorhexidine Oral Care
From Prevention of Pneumonia
to Risk Factor for Mortality

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Ventilator-Associated Pneumonia
Pathogenic mechanism

- Orogastric tube (to suction)
- Endotracheal tube
- Stomach
- Esophagus
- Trachea
- Pooled secretions
- Cuff


• RCT, double-blind, placebo-controlled
• Intervention: CHG 0.12% oral care
• Heart surgery patients
• Outcome:
  o Upper respiratory tract infection
  o Lower respiratory tract infection (!)
  o Antibiotic use
  o Mortality

- RCT, double-blind, placebo-controlled
- Intervention: CHG 0.12% oral care
- Heart surgery patients

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<th>Placebo (n=180)</th>
<th>Relative risk ratio (95% CI)</th>
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<td>0.20 (0.04 – 0.96)</td>
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</table>
Interpreting risk ratio’s, odds ratio’s, hazard ratio’s…

- **Basic principle:** risk ratio = “chance”
  
  Examples:
  - Chance of pneumonia when exposed to CHG
  - Chance of mortality when exposed to CHG

- **Risk = 1** → equal chance for CHG and non-CHG exposed

- **Risk > 1** (= increased risk for outcome)
  
  Example: mortality risk when exposed to CHG = 1.26

- **Risk < 1** (= reduced risk for outcome)
  
  Example: pneumonia risk when exposed to CHG = 0.84

*But is it statistically significant…?*
Confidence intervals: 95% certainty that risk is truly increased or decreased (=statistical significant)

4 possible situations...

Statistical intermezzo
Interpreting risk ratio’s, odds ratio’s, hazard ratio’s...

- RCT, double-blind, placebo-controlled
- Intervention: CHG 0.12% oral care
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Plenty of RCTs on CHG oral care

In various ICU patient populations
  - Heart surgery, general surgery, neurotrauma, medical, ... 

With various concentrations
  - 0.12%, 0.2%, 2%

With various outcomes
  - Respiratory tract infection, nosocomial pneumonia, VAP

With various results... (infection reduction, usually not stat. sign.)

- Meta-analysis of 14 RCTs
- Intervention: antiseptic oral care (12 studies: CHG)
- ICU patients (n=2481 of which 2341 in CHG trials)
- Outcome: VAP

### Chlorhexidine

<table>
<thead>
<tr>
<th>Antiseptic</th>
<th>Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>De Riso et al (1996)</td>
<td>3</td>
<td>173</td>
</tr>
<tr>
<td>Fourrier et al (2000)</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Houston et al (2002)</td>
<td>4</td>
<td>270</td>
</tr>
<tr>
<td>MacNaughton et al (2004)</td>
<td>32</td>
<td>91</td>
</tr>
<tr>
<td>Grap et al (2004)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Fourrier et al (2005)</td>
<td>13</td>
<td>114</td>
</tr>
<tr>
<td>Bopp et al (2006)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Koeman et al (2006)</td>
<td>13</td>
<td>127</td>
</tr>
<tr>
<td>Tantipong et al (2008)</td>
<td>5</td>
<td>102</td>
</tr>
<tr>
<td>Scannapieco et al (2009)</td>
<td>14</td>
<td>116</td>
</tr>
<tr>
<td>Bellisimo-Rodriguez et al (2009)</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Panchabhai et al (2009)</td>
<td>14</td>
<td>88</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1184</strong></td>
<td><strong>159</strong></td>
</tr>
</tbody>
</table>

Total events: 123

Heterogeneity: $\chi^2=0.66$, $df=11$ ($p=0.16$); $I^2=29$

Test for overall effect: $Z=2.40$ ($p=0.02$)

Test for subgroup differences: $\chi^2=0.86$, $df=1$ ($p=0.35$); $I^2=0$

(Reduced pneumonia risk)
• **Warnings…**
  
  o **Different CHG concentrations**
    - 0.12%  RR 0.73 (95% CI, 0.51 – 1.05)
    - 0.2%  RR 0.79 (95% CI, 0.46 – 1.36)
    - 2.0%  RR 0.53 (95% CI, 0.31 – 0.91)
  
  o **Different patient populations**
    - Cardiac surgery  RR 0.41 (95% CI, 0.17 – 0.98)
    - Mixed ICU  RR 0.77 (95% CI, 0.77 – 1.02)
    - Surgery or trauma  RR 0.38 (95% CI, 0.13 – 1.10)
• Despite overt limitations…
• Worldwide promoted in ICUs patients on mechanical ventilation (no discrimination)
• Essential part of ventilator bundles or VAP prevention bundles
  ➢ CDC, 2004 & SHEA, 2014 (US)
  ➢ Institute for Healthcare Promotion, 2012 (UK)
  ➢ IDSA/ATS, 2005
  ➢ Scottish Patient Safety Program, 2015
• In clinical practice…
  ➢ Use in non-ventilated patients
2014
Meta-analysis of 16 RCTs

Intervention: CHG oral care

ICU patients (n=3630)

Outcomes:

- Nosocomial pneumonia (broader than VAP)
- Mortality

- **Pneumonia risk** (16 RCTs)...
  - Cardiac surgery: RR 0.56 (95% CI, 0.41 – 0.77)
  - Non-cardiac surgery: RR 0.88 (95% CI, 0.66 – 1.16)

- **Mortality risk** (12 RCTs)...
  - All ICU patients: RR 1.13 (95% CI, 0.99 – 1.28)
    - Cardiac surgery: RR 0.88 (95% CI, 0.25 – 3.14)
    - Non-cardiac surgery: RR 1.13 (95% CI, 0.99 – 1.29)
• Network meta-analysis of 29 studies (11 CHG)
• Intervention: SDD, SOD, CHG oral care
• ICU patients (n=3630), with excl. of specialized populations such as cardiac surgery or LTx
• Outcomes: Mortality
<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Odds ratio, M-H random (95% CI)</th>
<th>Weight (%)</th>
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<tbody>
<tr>
<td>Fourier 2000</td>
<td>3/30 7/30</td>
<td></td>
<td>2</td>
<td>0.37 (0.08 to 1.58)</td>
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<td>29/101 29/93</td>
<td></td>
<td>8</td>
<td>0.89 (0.48 to 1.64)</td>
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<td>Total (95% CI)</td>
<td>367/1288 326/1330</td>
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Test for heterogeneity: $\tau^2=0.00$, $\chi^2=8.41$, df=10, P=0.59, $I^2=0\%$

Test for overall effect: $z=2.47$, P=0.01

(Decreased mortality risk with CHG) (Increased mortality risk with CHG)
Increased mortality risk with CHG

Decreased mortality risk with CHG

Reduced mortality risk with CHG oral care (not sign.)
Increased mortality risk with CHG oral care (statistically sign.)

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Decreased mortality risk with CHG

Increased mortality risk with CHG
• Retrospective cohort study
• Single center
• Assessing effect of ventilator bundle components on outcomes
• n=5536
• **Results:** Association between CHG oral care and ventilator mortality…
  - Patients on MV ≥3 days:   HR 1.63 (95% CI, 1.15 – 2.31)
2017
• International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

• CHG oral care for prevention of pneumonia

→ no recommendation
What about CHG oral care outside the ICU…?

• **Broad spectrum of indications**
  - Pneumonia prevention
  - Oral pathology (gingivitis, periodontitis, halitosis, …)
  - Standard care in patients with impaired functional status

• **Broad spectrum of patient populations**
  - ICU
  - Geriatrics
  - Onco-hematology
  - Trauma
  - ORL, …
What about CHG oral care outside the ICU...?

- **Systematic literature review...**
  - RCTs with CHG oral care vs. comparator
  - Non-ICU population
  - Mortality as endpoint

- **Results: no studies available**

S. Blot, unpublished data
Hospital-wide, retrospective, observational cohort study to assess the effect of CHG oral on mortality

Ghent University Hospital, 2012 – 2014
All adult patients (n=82,274)
CHG oral care exposure
  - No CHG oral care, n=71,141
  - Low exposure (cumulative dose ≤300 mg), n=8080
  - High exposure (cumulative dose >300 mg), n=3053

Note:
300 mg CHG = equivalent of 1 bottle of 250 mL oral care solution (0.12%)
Assumed to cover 5-6 days (15 mL per oral care provision, 3/day)
Adjustment through logistic regression for:

- Age
- Sex
- Emergency admission
- Medical / surgical admission (based on principle diagnosis and procedure)
- Diagnostic category (25 classes MDC, ICD-9-CM)
- Risk of mortality (All Patient-Refined-Diagnosis Related Groups, APR-DRG)
  - Categories: minor, moderate, major, extreme
## Mortality rates stratified for risk of mortality & CHG exposure

<table>
<thead>
<tr>
<th></th>
<th>High CHG exposure (&gt;300 mg)</th>
<th>Low CHG exposure (≤300 mg)</th>
<th>No CHG oral care</th>
<th>P</th>
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<td>571 / 3053 (18%)</td>
<td>870 / 8080 (11%)</td>
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<td>Mortality risk, category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1, minor (n=53 233)</td>
<td>4 / 450 (1%)</td>
<td>34 / 2 214 (2%)</td>
<td>53 / 50 569 (0.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2, moderate (n=19 154)</td>
<td>46 / 790 (6%)</td>
<td>161 / 3 050 (5%)</td>
<td>254 / 15 314 (2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3, major (n=7 417)</td>
<td>133 / 856 (16%)</td>
<td>273 / 1 874 (15%)</td>
<td>402 / 46 874 (9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4, extreme (n=2 470)</td>
<td>388 / 957 (41%)</td>
<td>402 / 942 (43%)</td>
<td>245 / 57 1 (43 %)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
• **All patients**: adjusted mortality risk (logistic regression analysis):
  
  - No CHG oral care Reference
  - Low CHG (≤300 mg) OR 2.6 (95% CI, 2.3 – 2.9)
  - High CHG (>300 mg) OR 2.7 (95% CI, 2.4 – 3.2)

  “Adjusted number needed-to-harm” to result in 1 extra fatality case: 47 (95% CI, 45 – 49)

**Adjusted mortality risk per risk of mortality category** (logistic regression analysis)

<table>
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<tr>
<th>Risk of Mortality</th>
<th>Low CHG (≤300 mg)</th>
<th>High CHG (&gt;300 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor/moderate risk of mortality, n=72,387</td>
<td>OR 5.5 (95% CI, 4.5 – 6.7)</td>
<td>OR 5.0 (95% CI, 3.5 – 6.9)</td>
</tr>
<tr>
<td>Major risk of mortality, n=7417</td>
<td>OR 2.3 (95% CI, 2.0 – 2.8)</td>
<td>OR 3.1 (95% CI, 2.5 – 3.9)</td>
</tr>
<tr>
<td>Extreme risk of mortality, n=2470</td>
<td>OR 1.1 (95% CI, 0.9 – 1.4)</td>
<td>OR 1.1 (95% CI, 0.9 – 1.4)</td>
</tr>
</tbody>
</table>
• **Adjusted mortality risk for various subgroups**
  (logistic regression analysis)

**Cardiothoracic & vascular surgery, n=1106**
- Low CHG (≤300 mg) OR 0.7 (95% CI, 0.2 – 2.9)
- High CHG (>300 mg) OR 1.0 (95% CI, 0.3 – 3.4)

**Non-ICU patients, n=69,208**
- Low CHG (≤300 mg) OR 4.9 (95% CI, 4.2 – 5.7)
- High CHG (>300 mg) OR 3.7 (95% CI, 2.8 – 4.8)

**Not ventilated ICU patients, n=9316**
- Low CHG (≤300 mg) OR 0.9 (95% CI, 0.6 – 1.1)
- High CHG (>300 mg) OR 1.0 (95% CI, 0.6 – 1.4)
• **Adjusted mortality risk for various subgroups** (logistic regression analysis)

**ICU patients, ventilated >96 hrs. n=903**
- Low CHG (≤300 mg): OR 1.5 (95% CI, 0.8 – 2.9)
- High CHG (>300 mg): OR 1.1 (95% CI, 0.6 – 2.1)

**ICU patients, ventilated ≤96 hrs., n=2847**
- Low CHG (≤300 mg): OR 0.6 (95% CI, 0.4 – 0.9)
- High CHG (>300 mg): OR 0.5 (95% CI, 0.3 – 0.8)
How to interpret…?

- Large study with high-quality data
- Strong relationship between CHG oral care & mortality
- Relationship particularly strong in patients with inherent favorable prognosis
- **Pathogenic mechanism** → increased mortality = unknown

Limitations

- Observational study
- No detailed length of exposure data (proxy by low/high exposure)
- Unable to compare higher CHG concentrations (≥0.2%)
Back to work… Essential questions:

① Is there a proven benefit of CHG oral care in this type of patient?

② If ‘yes’, does the benefit outweigh the eventual risk?

③ Irrespective of the proven benefit and the perceived risk of mortality… Is there any alternative?
Take-home message

“These findings incite reconsideration of the practice of CHG oral care in patient populations for which an evidence-based benefit is lacking.”
Controversial viewpoints

Should CHG oral care be abandoned?

Klompas & Bouadma. Intensive Care Med 2018
Ricard & Lisboa. Intensive Care Med 2018

EDITORIAL

Oral care with chlorhexidine: beware!

EDITORIAL

Caution for chlorhexidine gluconate use for oral care: insufficient data

Klompas & Bouadma. Intensive care Med 2018
Ricard & Lisboa. Intensive Care Med 2018
How we deal with research results we do not understand...

CHG oral care...

- (might) reduce pneumonia risk → excessive promotion
- (might) reduce mortality → lots of methodological concerns

- Do we react differently according to studies with a positive vs. negative message?

Or is it the absence of a clear pathogenic mechanism that makes us questioning the research findings?
Association of blood transfusion from female donors with and without a history of pregnancy with mortality among transfusion recipients

Caram-Deelder C, et al. JAMA 2017

- Retrospective multicenter cohort study (n=31,118)

**Associations with mortality for female recipients**

<table>
<thead>
<tr>
<th>Male donor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-pregnant female donor</td>
<td>HR 0.96 (95% CI, 0.89 – 1.03)</td>
</tr>
<tr>
<td>Ever-pregnant female donor</td>
<td>HR 0.99 (95% CI, 0.93 – 1.07)</td>
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</table>

**Associations with mortality for male recipients**

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<td>HR 1.08 (95% CI, 1.02 – 1.15)</td>
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A call for unprejudiced interpreting

The CHG oral care case
1. Limited evidence of reduced pneumonia risk in cardiosurgical patients
2. Applied to other patient population without evidence
3. Initial neglect of an RCT showing increased mortality. Why?
   - No reasonable explanation?
   - Incidental finding?
4. CHG oral care is harmful: accumulating evidence from meta-analyses and large cohort studies
5. Evidence pneumonia reduction = evidence mortality increase
6. Still…

- Beware of over-interpreting what we like
- Positive result…? Beware of absence of AEs data
Thank you

Sigma Theta Tau Awards Committee
for granting me the honor of the
Baxter International Foundation’s Episteme Award

Dept. of Internal Medicine & Pediatrics, Faculty of Medicine & Health Science, Ghent University, Flanders
Burns, Trauma & Critical Care Research Centre, The University of Queensland, Brisbane, Australia
stijn.blot@UGent.be