Sepsis Management Update 2014

Laura J. Moore, MD, FACS
Associate Professor, Department of Surgery
The University of Texas Health Science Center, Houston
Medical Director, Shock Trauma ICU
Texas Trauma Institute, Memorial Hermann Hospital
Objectives

Discuss 2014 Surviving Sepsis Campaign Guidelines
Sepsis Screening
Use of Procalcitonin
Norepinephrine as first line vasopressor
Fluid resuscitation

Review recently published ProCESS study
Revision of the 2008 Surviving Sepsis Campaign (SSC) Guidelines
Six hour “resuscitation” bundle

- Central venous pressure 8 – 12 mm Hg
- Mean arterial pressure (MAP) ≥ 65 mm Hg
- Urine output ≥ 0.5 ml/kg/hr
- Central venous or mixed venous oxygen saturation 70% or 65% respectively
- *In patients with elevated lactate levels target resuscitation to normalize lactate*
## Table 5. Hospital Mortality and Length of Stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lactate Clearance Group (n = 150)</th>
<th>ScvO₂ Group (n = 150)</th>
<th>Proportion Difference (95% Confidence Interval)</th>
<th>P Value⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent to treat</td>
<td>25 (17)</td>
<td>34 (23)</td>
<td>6 (-3 to 15)</td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
<td>25 (17)</td>
<td>33 (22)</td>
<td>5 (-3 to 14)</td>
<td></td>
</tr>
<tr>
<td>Length of stay, mean (SD), d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>5.9 (8.46)</td>
<td>5.6 (7.39)</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>11.4 (10.89)</td>
<td>12.1 (11.68)</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Hospital complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days, mean (SD)</td>
<td>9.3 (10.31)</td>
<td>9.9 (11.09)</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>Multiple organ failure, No. (%)</td>
<td>37 (25)</td>
<td>33 (22)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>Care withdrawn, No. (%)</td>
<td>14 (9)</td>
<td>23 (15)</td>
<td>.15</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; ScvO₂, central venous oxygen saturation.

a Primary study end point.

b Continuous data are compared using an unpaired t test; categorical variables, using the χ² test.
Surviving Sepsis Campaign Guidelines 2012

Grades of Evidence

Grade 1A
- Glucose protocol (<180)
- Vent weaning
- SBT protocol
- Sedation protocol
- No renal dose dopamine
- No high-dose steroids
- Low tidal volume for ALI

Grade 1B
- Broad-spectrum antibiotics within 1 hour
- De-escalate antibiotics
- Initial resus with crystalloid
- Avoid hetastarch
- Norepinephrine 1st Line Pressor
- Avoid bicarbonate
- DVT/PUD prophylaxis
- Dobutamine for cardiac dysfunction

Grade 1C
- Avoid paralysis in absence of ARDS
- Early goal-directed therapy
- Cultures before antibiotics
- Early source identification
- Source control within 12 hours
- Consider limiting support
- 30 cc/kg IBW bolus for shock
- Conservative fluids for ARDS
- Avoid phenylephrine
- Screening for Sepsis

### Surviving Sepsis Campaign Guidelines 2012

#### Grades of Evidence

<table>
<thead>
<tr>
<th>Grade 1A</th>
<th>Grade 1B</th>
<th>Grade 1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose protocol (&lt;180)</td>
<td>Broad-spectrum antibiotics within 1 hour</td>
<td>Avoid paralysis in absence of ARDS</td>
</tr>
<tr>
<td>Vent weaning SBT protocol</td>
<td>De-escalate antibiotics</td>
<td>Early goal-directed therapy</td>
</tr>
<tr>
<td>Sedation protocol</td>
<td>Initial resus with crystalloid</td>
<td>Cultures before antibiotics</td>
</tr>
<tr>
<td>No renal dose dopamine</td>
<td>Avoid hetastarch</td>
<td>Early source identification</td>
</tr>
<tr>
<td>No high-dose steroids</td>
<td>Norepinephrine 1st Line Pressor</td>
<td>Source control within 12 hours</td>
</tr>
<tr>
<td>Low tidal volume for ALI</td>
<td>Avoid bicarbonate</td>
<td>Consider limiting support</td>
</tr>
<tr>
<td>DVT/PUD prophylaxis</td>
<td>Dobutamine for cardiac dysfunction</td>
<td>30 cc/kg IBW bolus for shock</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conservative fluids for ARDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid phenylephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening for Sepsis</td>
</tr>
</tbody>
</table>

Rationale: Early intervention is dependent upon the early identification of sepsis.

Early initiation of evidence based care has been shown to improve outcomes and decrease sepsis related mortality.
Three Step Sepsis Screening Tool
Done Twice Each Day

SICU Bedside Nurse
SIRS score

current heart rate ______ time ______
T min ______ time ______
T max ______ time ______
current resp rate ______ time ______
latest WBC count ______ date, time ______

points 0 1 2 3 4
heart rate (bpm) 70 - 109 55 - 69 40 - 54 ≤ 39 ≥ 180
T (°C) min max 36 - 38.4 34 - 35.9 32 - 33.9 30 - 31.9 ≤ 29.9
T (°F) min max 98.6 - 101.1 93.1 - 96.6 89.6 - 93.0 86 - 89.5 ≤ 85.9
resp rate (br / min) 12 - 24 10 - 11 6 - 9 35 - 49 ≤ 5 ≥ 50
latest WBC (kcell / mm³) 3 - 14.9 15 - 19.9 20 - 39.9 ≤ 1 ≥ 40
score (total points)

If SIRS score ≥ 4, then notify SICU Nurse Practitioner to complete sepsis screening form.

☐ SICU
☐ overflow ☐ MICU ☐ NICU ☐ CCU

Completed by: ______________ RN Date / time: ______________

Performance improvement review by SICU Medical Director or designee:

☐ sepsis (Phase 1) ☐ severe sepsis (Phase 2) ☐ septic shock (Phase 2)

Start sepsis management protocol ☐ Yes ☐ No

Comments:

__________________________________________________________

Signature: ______________ MD Date / time: ______________

This form is not a part of the patient’s medical record.
Return all completed forms to SICU Nurse Practitioner office.

SICU Nurse Practitioner
Sepsis Screening

1. Vascular access?
   type: dialysis triple / quad PICC port tunneled other (IV, art)
   site
   local finding
   blood culture finding
   Yes No

2. Clinical pulmonary infection score (CPIS)
   variable temperature (°C) points score
   time (hmm)
   36.5 - 38.4 0
   38.5 - 39.9 1
   > 39.0 or < 36.0 2
   blood leukocyte count (# per mm³) time (hmm)
   4,000 - 11,000 0
   < 4,000 or > 11,000 1
   tracheal secretions time (hmm)
   small 0
   moderate 1
   large 2
   purulent (add 1 point if purulent) +1
   oxygenation (PaO2/FiO2) time (hmm)
   ≥ 240 or presence of ARDS 0
   < 240 and absence of ARDS 2
   chest radiograph time (hmm)
   no infiltrate 0
   patchy or diffuse infiltrate 1
   localized infiltrate 2

3. Abdomen
   recent abdominal surgery? Yes No
   abdominal pain? Yes No
   abdominal distention? Yes No
   purulent drainage from surgical drains? Yes No
   intolerance to enteral nutrition? Yes No

4. Skin / soft tissue
   erythema / drainage from other surgical site? Yes No
   site

5. Urinary tract
   urinary catheter? Yes No
   date placed
   latest urinalysis / urine culture results

6. Other site
   site

Completed by: ______________ NP Date / time: ______________

Suspicion of:
    line infection?
    Yes No

Intubated / mech vent support?
    Yes No

date intubated:

pneumonia?
    Yes No

cellulitis / soft tissue infection?
    Yes No

UTI?
    Yes No

other infection?
    Yes No
Validation of a Screening Tool for the Early Identification of Sepsis

Laura J. Moore, MD, Stephen L. Jones, MD, Laura A. Kreiner, MD, Bruce McKinley, PhD, Joseph F. Sucher, MD, S. Rob Todd, MD, Krista L. Turner, MD, Alicia Valdivia, RN, and Frederick A. Moore, MD

The Journal of TRAUMA® Injury, Infection, and Critical Care

Early Screening and Implementation of Evidence Based Care

TMH Performance Improvement
Mortality for Severe Sepsis/Septic Shock by Unit

<table>
<thead>
<tr>
<th></th>
<th>2006 Mortality</th>
<th>2007 Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surg ICU</td>
<td>35.1%</td>
<td>23.3%</td>
</tr>
<tr>
<td>ER</td>
<td>25.0%</td>
<td>30.3%</td>
</tr>
<tr>
<td>CV ICU</td>
<td>21.4%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Med ICU</td>
<td>38.0%</td>
<td>37.2%</td>
</tr>
</tbody>
</table>
Objectives

Discuss 2014 Surviving Sepsis Campaign Guidelines

Sepsis Screening
Use of Procalcitonin
Norepinephrine as first line vasopressor
Fluid resuscitation

Review recently published ProCESS study
What is procalcitonin?

• 116-amino acid peptide
• Biomarker that responds to both infection & inflammation
• Can it be used to differentiate sepsis from SIRS?
• Could this be of benefit in sepsis identification?
Should Procalcitonin be Introduced in the Diagnostic Criteria for the Systemic Inflammatory Response Syndrome and Sepsis?

Evangelos J. Giamarellos-Bourboulis, Panagiota Giannopoulou, Paraskevi Grecka, Dionyssios Voros, Konstantinos Mandragos, and Helen Giamarello

Journal of Critical Care, Vol 19, No 3 (September), 2004: pp 152-157

Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis

Bernard Uzzan, MD; Régis Cohen, MD, PhD; Patrick Nicolas, PharmD, PhD; Michel Cucherat, MD; Gérard-Yves Perret, MD, PhD

Crit Care Med 2006 Vol. 34, No. 7

Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean

Lancet Infect Dis 2007; 7: 210-17
Procalcitonin does not CLEARLY differentiate between the acute inflammatory pattern of sepsis and other causes of generalized inflammation (such as post-operative inflammation)
Objectives

Discuss 2014 Surviving Sepsis Campaign Guidelines

- Sepsis Screening
- Use of Procalcitonin
- Norepinephrine as first line vasopressor
- Fluid resuscitation

Review recently published ProCESS study
Surviving Sepsis Campaign Guidelines 2012

Grades of Evidence

Grade 1A
- Glucose protocol (<180)
- Vent weaning SBT protocol
- Sedation protocol
  - No renal dose dopamine
  - No high-dose steroids
  - Low tidal volume for ALI

Grade 1B
- Broad-spectrum antibiotics within 1 hour
- De-escalate antibiotics
- Initial resus with crystalloid
- Avoid hetastarch
- Avoid bicarbonate
- DVT/PUD prophylaxis
- Norepinephrine 1st Line Pressor
- Avoid phenylephrine
- Dobutamine for cardiac dysfunction

Grade 1C
- Avoid paralysis in absence of ARDS
- Early goal-directed therapy
- Cultures before antibiotics
- Early source identification
- Source control within 12 hours
- Consider limiting support
- 30 cc/kg IBW bolus for shock
- Conservative fluids for ARDS
- Avoid phenylephrine
- Screening for Sepsis

Vasopressors

- Target mean arterial pressure of 65 mmHg
- Norepinephrine is now 1st choice
- Vasopressin 0.03 units/minute can be added to norepinephrine
- Vasopressin should not exceed 0.04 units/minute
- Dopamine only in highly selective patients
**TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed Risk</th>
<th>Corresponding Risk</th>
<th>Relative Effect (95% CI)</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term mortality</strong></td>
<td>Dopamine</td>
<td>Norepinephrine</td>
<td>RR 0.91 (0.83 to 0.99)</td>
<td>2043 (6 studies)</td>
<td>☄️ ☄️ ☄️ ☄️ moderate³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>530 per 1000</td>
<td>482 per 1000 (440 to 524)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td>RR 0.47 (0.38 to 0.58)</td>
<td>1931 (2 studies)</td>
<td>☄️ ☄️ ☄️ moderate³</td>
<td></td>
</tr>
<tr>
<td>— Supraventricular arrhythmias</td>
<td>229 per 1000</td>
<td>82 per 1000 (34 to 195)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td>RR 0.35 (0.19 to 0.66)</td>
<td>1931 (2 studies)</td>
<td>☄️ ☄️ ☄️ moderate³</td>
<td></td>
</tr>
<tr>
<td>— Ventricular arrhythmias</td>
<td>39 per 1000</td>
<td>15 per 1000 (8 to 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = confidence interval, RR = risk ratio.

Strong heterogeneity in the results ($I^2 = 85\%$), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.

Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.
Objectives

Discuss 2014 Surviving Sepsis Campaign Guidelines

- Sepsis Screening
- Use of Procalcitonin
- Norepinephrine as first line vasopressor
- Fluid resuscitation

Review recently published ProCESS study
Surviving Sepsis Campaign Guidelines 2012

Grades of Evidence

Grade 1A
- Glucose protocol (<180)
- Vent weaning SBT protocol
- Sedation protocol
- No renal dose dopamine
- No high-dose steroids
- Low tidal volume for ALI

Grade 1B
- Broad-spectrum antibiotics within 1 hour
- De-escalate antibiotics
- Initial resus with crystalloid
- Avoid hetastarch
- Norepinephrine 1st Line Pressor
- Avoid bicarbonate
- DVT/PUD prophylaxis
- Dobutamine for cardiac dysfunction

Grade 1C
- Avoid paralysis in absence of ARDS
- Early goal-directed therapy
- Cultures before antibiotics
- Early source identification
- Source control within 12 hours
- Consider limiting support
- 30 cc/kg IBW bolus for shock
- Conservative fluids for ARDS
- Avoid phenylephrine
- Screening for Sepsis

Fluid Resuscitation in Sepsis

- Crystalloids are the first line agent
  - Absence of clear benefit with colloids
  - ALBIOS showed improved survival with albumin in septic shock subgroup

- Recommend 30 cc/kg IBW for shock

- Avoid hydroxyethyl starch solutions
Why not HES?

**CRYSTMAS**: septic shock patients, no difference in mortality with HES vs. 0.9% NS (31% vs. 25.3%, \( p = 0.37 \)); however the study was underpowered to detect the 6% difference in absolute mortality observed.

**6S Trial**: septic patients, *increased mortality rates with 6% HES* vs Ringer’s acetate (51% vs. 43% \( p = 0.03 \)).

**CHEST**: ICU patients, no 90-d mortality difference with 6% HES vs. 0.9% NS, \( n = 7000 \) (18% vs. 17%, \( p = 0.26 \)); the need for renal replacement therapy was higher in the HES group (7.0% vs. 5.8%; RR 1.21; 95% CI 1.00–1.45; \( p = 0.04 \)).

**CRISTAL**: ICU pts, crystalloid vs. any colloids, Europe, \( n=2857 \) pts, no difference in mortality
1818 severe sepsis cases, 100 hospitals

Randomized to albumin or crystalloid
Study design

Pts. with severe sepsis or septic shock (6-24 hr)

Positioning of arterial and central venous line (if not performed earlier)

Randomization

Volume replacement
[Rivers’ protocol]

Albumin:
[300 ml at 20% in 3* hrs] + crystalloids

Crystalloids
from day 1 to day 28 (or ICU discharge if earlier)

Albumin

Plasmatic level of Albumin

≥ 30 g/L

No infusion of Albumin

< 30 g/L and
≥ 25 g/L

Infusion of Albumin:
200 ml at 20% in 3* hrs

< 25 g/L

Infusion of Albumin:
300 ml at 20% in 3* hrs

N.B.: if not available, please refer to the last value available of plasmatic level of albumin
Overall population (1810 pts)

90-day mortality: 41.1% vs. 43.6% (P=0.29)

Log-rank P=0.39
Pts with septic shock as defined according to the SOFA score
(3°/4°)
(pts = 1135)

Probability of Survival

Days since Randomization
Conclusions

In patients with sepsis albumin infusion compared to crystalloids alone provided hemodynamic advantages, and more favorable fluid balance without survival benefits.

In patients with septic shock, as recognized at entry, hemodynamic fluid balance advantages were greater than in general population and, in addition, these patients survived significantly more at 90 days.
Objectives

Discuss 2014 Surviving Sepsis Campaign Guidelines
Sepsis Screening
Use of Procalcitonin
Norepinephrine as first line vasopressor
Fluid resuscitation

Review recently published ProCESS study
Study Objectives:
- To determine if early goal directed therapy (EGDT) as described by Rivers et al is generalizable
- To determine which EGDT protocol elements are necessary
### Assigned Interventions

**Procedure: Early Goal Directed Therapy (EGDT)**
Subjects will have a CVC inserted for continuous monitoring of their CVP and Scv02. Early structured treatment will be provided based on subjects' CVP, mean arterial pressure (MAP) and Scv02 measurements.

**Procedure: Protocolized Standard Care (PSC)**
Routine equipment will be used to monitor subjects' blood pressure and oxygen levels. Early structured treatment is based on the subjects' systolic blood pressure and the study doctors' judgment of fluid status and perfusion status.

**Procedure: Usual Care (UC)**
Attending physicians will provide routine care to subjects. Study measurements and treatments will be based on the physicians/sites' standard practices.

Validation Study
Multicenter Trial
20 sites

*ProCESS*
Protocolized Care for Early Septic Shock
NIH-sponsored
$8.4 Million

Derek Angus et al.
Univ. of Pittsburgh
ProCESS EGDT

- Similar to Rivers protocol
- Same goal as Rivers protocol:
  - ScvO2 ≥ 70%
  - Blood tx to keep Hct > 30%
  - No arterial line
Protocolized Standard Care

- No CVP monitoring
- No central venous oximetric catheter
- No ScvO2 goal
- SBP/perfusion monitoring
- Target Hb 7 g/dL
- No arterial line
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

• N=1341, 31 U.S. Emergency Depts
• Protocol-based EGDT, n=439
• Protocol-based standard therapy, n=446
• Usual care, n=456
Mortality at 60 days:

- Protocol-based EGDT group (21.0%)
- Protocol-based standard-therapy group (18.2%)
- Usual-care group (18.9%)

Protocol-based therapy vs. usual care
- RR 1.04; 95% CI, 0.82 to 1.31; P = 0.83

Protocol-based EGDT vs. protocol-based standard therapy
- RR 1.15; 95% CI, 0.88 to 1.51; P = 0.31

No significant differences in 90-day mortality, 1-year mortality, or the need for organ support.
**Table 1. Differences in Mortality and Key Clinical Values in the EGDT Study and the ProCESS Study.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>EGDT Study</th>
<th>ProCESS Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGDT Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Predicted mortality on the basis of APACHE II score (%)</td>
<td>40.3</td>
<td>36.9</td>
</tr>
<tr>
<td>Actual mortality (%)</td>
<td>30.5</td>
<td>46.5</td>
</tr>
<tr>
<td>Lactate (mmol/liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 0 hr</td>
<td>7.7</td>
<td>6.9</td>
</tr>
<tr>
<td>At 6 hr</td>
<td>4.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Central venous oxygen saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 0 hr</td>
<td>48.6</td>
<td>49.2</td>
</tr>
<tr>
<td>At 6 hr</td>
<td>77.3</td>
<td>66.0</td>
</tr>
<tr>
<td>Central-catheter rate at 6 hr (%)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*APACHE denotes Acute Physiology and Chronic Health Evaluation, NA not applicable, and NR not reported.

*Average amount of crystalloids given in first 6 hours by group*

EGDT  2.8 Liters
PSC  3.3 Liters
UC  2.3 Liters
ProCESS: Cumulative Mortality

A Cumulative In-Hospital Mortality to 60 Days

Rivers EGDT 30.5% in-hospital mortality

B Cumulative Mortality to 1 Yr

P = 0.52 by log-rank test

No. at Risk
Protocol-based EGDT 439 373 356 348 347 347 347
Protocol-based standard therapy 446 389 376 368 366 366 365
Usual care 456 396 376 371 371 371 370

P = 0.70 by log-rank test, 90 days
P = 0.92 by log-rank test, 1 yr

No. at Risk
Protocol-based EGDT 439 289 217 194 175 156 145
Protocol-based standard therapy 446 308 212 196 179 158 142
Usual care 456 285 211 199 181 164 139

ProCESS Investigator
Conclusions

Protocol-based resuscitation of patients diagnosed with septic shock in the ER did not improve outcomes.
ProCESS Investigator
Conclusions

Protocol-based resuscitation of patients diagnosed with septic shock in the ER did not improve outcomes.

SHOULD WE ABANDON EGDT???
Important Caveats

• Patients in all groups received an average of > 2 liters of fluid
• >75% of patients received antibiotics prior to randomization into the study
• The 18% mortality rate in the “usual care” groups is much lower than the septic shock mortality rate of 46.5% reported in Rivers original trial
• The majority of patients had central lines inserted
Should we abandon EGDT?

• Early diagnosis and early intervention remain critical

• Two large ongoing trials may clarify
  – ARISE (Australian Resuscitation in Sepsis Evaluation RCT)
  – ProMISe (Protocolised Management in Sepsis Trial)
Summary

- Sepsis screening aids in early recognition
- Early, evidence based care is critical
- Procalcitonin is non-specific, not useful
- Norepinephrine is now first line agent
- Fluid bolus 30 cc/kg IBW for septic shock
- ProCESS study has limitations
QUESTIONS?