Evaluation and Management of Sepsis: Identification & Treatment Bundles

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Severe Sepsis: Defining a Disease Continuum

Infection or Trauma → SIRS → Sepsis → Severe Sepsis

Adult Criteria
A clinical response arising from a nonspecific insult, including ≥ 2 of the following:
- Temperature: > 38°C or < 36°C
- Heart Rate: > 90 beats/min
- Respiration: > 20/min
- WBC count: > 12,000/mm³, or < 4,000/mm³, or > 10% immature neutrophils

SIRS = Systemic Inflammatory Response Syndrome

Signs & Symptoms of Sepsis

- Chills
- Alteration in LOC
- Tachypnea
- Unexplained metabolic acidosis
- ↑ Heart rate
- Altered blood pressure
- ↓ Platelets
- ↑ Bands
- ↓ Skin perfusion
- ↓ Urine output
- Skin mottling
- Poor capillary refill
- Hyperglycemia
- Purpura/petechia

Severe Sepsis: Defining a Disease Continuum

**Infection or Trauma**

**SIRS**

**Sepsis**

**Severe Sepsis**

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SIRS with a presumed or confirmed infectious process

Examples:
- Cardiovascular (refractory hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

Shock

SEPSIS SCREEN (To be completed every shift)

A. Infection
- Does patient have an infection or suspicion of infection?
- Is patient on antibiotics (not prophylaxis)?

If No, Stop Here

B. SIRS (Systemic Inflammatory Response Syndrome)

Does patient have 2 or more of the following SIRS criteria?
- T > 38 (100.4) or < 36 (96.8)
- HR > 90 BPM
- RR > 20 breaths/min
- WBC > 12,000, < 4,000, or > 10% immature neutrophils

C. Acute Organ Dysfunctions

Does patient meet one or more of the following criteria?
- SBP < 90 mmHg or MAP < 65 mmHg
- SBP decrease > 40 mmHg from baseline
- Bilateral pulmonary infiltrates with a new (or increased) oxygen requirement to maintain SpO₂ > 90%
- Bilateral pulmonary infiltrates with PaO₂/FiO₂ ratio < 300
- Creatinine > 2.0 mg/dl or Urine Output < 0.5 ml/kg/hour for > 2 hours
- Bilirubin > 2 mg/dl
- Platelet count < 100,000
- Lactic acidosis (LAC > 1.5 or pCO₂ > 40 mmHg)

- Altered consciousness or reduced GCS

If all criteria met for A, B & C, screen is positive for severe sepsis

Time: __________ Time: __________ Time: __________

☐ Treatment in Place

☐ New positive screen for severe sepsis

☐ MD notified Time: ____________________

☐ HRT team notified Time: __________

Routine Screening is Necessary to Launch the Evidence Based Care = Bundles
IHI/VHA Change Strategy = Bundles

- Care Bundles
  - Grouping of care elements for particular symptoms, procedures or treatments
  - Strong science, good methodology, poor process
  - Bundle characteristics
    - Solid evidence
    - Relatively easy & inexpensive
    - Individual components defined well
    - Process not defined well
  - All parts of the bundle (sets of practice) must be implemented to be successful
Benefits of Bundles

- All or none assessment of process quality represents an important advance in the level of patient centeredness and system-mindedness of performance measures & reporting
- Multiple studies have demonstrated the impact of bundles.
- Implementation of bundles have routinely demonstrated an improvement in patient outcome and reduced resource utilization.
- Bundles have become so successful that their use could be considered a standard of care.


Bundles Utilize the Natural Strengths of Clinicians

- All hospitals have clinicians that are wonderfully talented. However, these clinicians often are not empowered to utilize their talents
- Bundles are designed to help empower clinicians to act quickly and utilize their clinical skills
- Using the skills of the clinical and administrative staff to best identify how to implement bundles at their facility increases the chance of success in improving outcomes.
References

The following is a small sample of the wonderful work that has been performed by scientists and clinicians. There are many other excellent publications available besides those listed here. For more information on any topic, a search of the National library of Medicine’s web site at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed) is suggested.


The Severe Sepsis Bundles: Surviving Sepsis Campaign/IHI

**Resuscitation Bundle**
(To be accomplished as soon as possible and scored over first 6 hours):
- Serum lactate measured.
- Blood cultures obtained prior to antibiotics administered. (1C)
- Perform imaging studies promptly to fine source (1C)
- From the time of presentation, broad-spectrum antibiotics within 3 hours for ED admissions and 1 hour for non-ED ICU admissions. (1D/1B)
- For hypotension and/or lactate > 4 mmol/L:
  - Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent) (1C)
  - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP ≥ 65 mmHg.
- For persistent hypotension despite initial fluid resuscitation (septic shock) and/or lactate > 4 mmol/L; (1C)
  - Achieve CVP > 8 mmHg & MAP ≥ 65 mmHg & UO > 0.5 ml/kg/hr
  - Achieve ScvO2 of ≥ 70% or SvO2 ≥ 65%.
  - If ScvO2 not ≥ 70% blood or dobutamine (2C)

**Management Bundle**
(To be accomplished as soon as possible and scored over first 24 hours):
- Tidal volume 6 ml/kg (1B) Inspiratory plateau pressures < 30 cmH2O for mechanically ventilated patients. (1C)
- Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy. (Given to patients with sepsis induced organ dysfunction at high risk of death (2B)
- Low-dose steroids administered for septic shock in accordance with a standardized ICU policy. (Given to patients who respond poorly to fluids or vasopressors) (2C)
- Glucose control maintained to < 150 mg/dL (8.3 mmol/L). (2C)

Adapted from the revised guidelines: CCM 2008;36:296-327.

Bleeding is the most common adverse effect associated with Xigris therapy. See Important Safety Information in this presentation.
Which components of the bundle do you believe will encounter the most resistance?

PROMPT AGGRESSIVE RESUSCITATION

“Early Goal Directed Therapy”
Early Goal Directed Therapy

Methodology: 263 severe sepsis patients

- Early Goal-Directed Therapy (EGDT)
  - Continuous ScvO2 monitoring & tx with fluids, blood, inotropes &/or vasoactives to maintain:
    - ScvO2 >70%, SaO2 > 93%, Hct ≥ 30%, CI/VO2
    - CVP ≥ 8-12
    - MAP ≥ 65
    - UO ≥ .5ml/kg/hr

- Standard Therapy
  - CVP ≥ 8-12
  - MAP ≥ 65
  - UO ≥ .5ml/kg/hr


Early Goal-Directed Therapy Results

28-day Mortality

- Standard Therapy: 49.2%, P = 0.01*
- EGDT: 33.3%

NNT = 7-8

*Key difference was in sudden CV collapse, not MODS

Evidence of Early Goal Directed Therapy

• First 6 hours of EGDT:
  – 1500cc more fluid
  – 64% received blood products vs. 18.5%
  – 13.7% received inotropes vs. 0.8%
  – No difference in vasopressor use or mechanical ventilation


Initial Resuscitation (1C)

- Protocolized resuscitation should begin as soon as sepsis induced tissue hypoperfusion is recognized or
- Elevated Serum lactate identifies tissue hypoperfusion in patients at risk who are not hypotensive
- Initial fluid challenges be started at > 1000 mL or 300-500 mL of colloid over 30 minutes (1C)

Serum Lactate is Associated with Mortality in Severe Sepsis Independent of Organ Failure and Shock

Objective:
- Test whether the association between initial serum lactate level and mortality in patients presenting to the ED with severe sepsis is independent of organ dysfunction and shock

Design:
- Retrospective, single center cohort study
- Academic teaching hospital

Patients:
- 830 adults admitted with severe sepsis in the ED
- Stratified lactate into 3 groups: low (<2), intermediate (2-3.9) and high (≥ or equal to 4)

Results:
- Intermediate and high serum lactate significantly associated with mortality regardless of the presence of shock or other organ dysfunction
- A single serum lactate seems to risk-stratify patients independent of organ dysfunction or hemodynamic instability

Mikkelsen, Mark et al CCM 2009 Vol 37 No 5
Early Goal-Directed Therapy: SSC Recommendations

• Goals of therapy within first 6 hours are: (1C)
  • Central Venous Pressure ≥ 8 - 12 mmHg
  • Mean arterial pressure ≥ 65 mmHg
  • Urine output ≥ 0.5 mL/kg/hr
  • ScvO₂ ≥ 70%; if not achieved with fluid resuscitation during first 6 hours (2C)
    - Transfuse PRBC to hematocrit >27% and/or
    - Administer dobutamine (max 20 mcg/kg/min) to goal


Potential Emergency Department Challenges

• Screening in Triage
• Drawing lactic acid level with less than one hour turn around time
• When and who will place the central line? Physician skill level?
• Monitoring CVPs and ScvO2-nurses skill level and available resources?
• When to transfer to ICU? ED-ICU handoff
• If long ED LOS---does the ED implement both resuscitation and management bundles
Controversies/Challenges

• Why did patients improve with EGDT
  – Tissue oxygenation target
    • Lactate
    • ScvO2
  – Inaccuracy of CVP measurement
    • Monitor readings
    • Poor correlation with volume and flow

• Use of tight glycemic control
  – Potential danger of hypoglycemia
  – Outcome benefits

• Use of aPC
  – Who should receive?
  – Cost
  – Complications

Clinical Investigations

The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis

Alan E. Jones, MD; Michael D. Brown, MD, VSc; Stephen Trzeciak, MD, MPH;
Nathan I. Shapiro, MD, MPH; John S. Garrett, MD; Alan C. Hoffer, MD; Jeffrey A. Kline, MD;
on behalf of the PROWESS/SHOCK investigators
Peer Review Publications

Odds Ratio (95% CI)

Gao, 2005
Sebat, 2005
Kuriyem, 2006
Shapiro, 2005
Trzebiath, 2006
Micek, 2006
Shi-yuan Lin, 2004
Qu, 2006
Nguyen, 2007
Jones, 2007
Sebat, 2007
Akinnusi, 2007
Rivers, 2001

Total:

Favors No EGDT
Favors EGDT

Before 1104 After 1175

Abstracts and Publications

Rivers, 2001
Publications
Abstracts

1 of every 6 Patients

Number Need To Treat

4125 Before 3328 After
### Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: Results of a three-year follow-up quasi-experimental study

Alvaro Castellanos-Ortega, MD, PhD; Borja Suberviola, MD; Luis A. Garcia-Ardudillo, MD; Maria S. Holanda, MD; Fernando Ortiz, MD; Javier Llano, MD, PhD; Miguel Delgado-Rodriguez, MD, MPH, PhD

- Prospective/Retrospective evaluation of impact of bundles on mortality
- 384 adults patients with Septic Shock enrolled after comprehensive education & process changes vs. 96 historical controls

### Results
- In hospital mortality 57.3% vs. 37.5% in the intervention group (p=0.001) (even after controlling for confounding variables)
- Lower HOS LOS (2 days) & ICU LOS 1 day
- Survival related to # of bundle component in compliance
- 6 or more in the resuscitation independent predictor of survival p > .001
- ScVO2 only single predictor with impact on mortality (p=.04)

Critical Care Medicine, 2010;38;1036-1043

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### Antibiotic Therapy

- Start intravenous antibiotic therapy within the first hour of recognition of severe sepsis after obtaining appropriate cultures (1D) for Septic shock (1B)
- Board spectrum: include one or more agents active against likely bacterial/fungal pathogens, & with good penetration into presumed source (1B)
- Reassess regimen daily to optimize efficacy, prevent resistance, avoid toxicity & minimize costs. (1C)

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

Effective antimicrobial administration within the 1st hour of documented hypotension was associated with increased survival in patients with septic shock.

*Each hour of delay over the next 6 hours was associated with an average decrease in survival of 7.6% (range 3.6-9.9%)

CCM 2006 Vol. 34 No.6

Mortality as a Function of Adequacy of Empiric Antimicrobial Therapy

Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department

David F. Gaineski, MD; Mark E. Mikkelsen, MD, MSCE; Roger A. Barad, MD; Jessica M. Pines, MD, MBA, MSCE; Richard Massone, MD; Frances F. Funia, MD; Frances S. Shaffer, PhD; Munish Goyal, MD

Antibiotic Challenges

- Appropriate selection – determined based upon consensus guidelines and pathogen sensitivity at your institution

- Timing issues
  - How? Delivery time challenges of antibiotics
  - Possible solutions

< 1hr (mortality 19.5 vs. 33.2%; odds ratio, 0.30 [CI, 0.11-0.83]; p=.02)

< 1hr (mortality 25 vs. 38.5%; odds ratio, 0.50 [CI, 0.27-0.92]; p=.03)
Management Bundle Components

Controversies/Challenges

- Why did patients improve with EGDT
  - Tissue oxygenation target
    - Lactate
    - ScvO2
  - Inaccuracy of CVP measurement
    - Monitor readings
    - Poor correlation with volume and flow
- Use of aPC
  - Who should receive?
  - Cost
  - Complications
- Use of tight glycemic control
  - Potential danger of hypoglycemia
  - Outcome benefits
Recombinant human Activated Protein C (2B)

- Recombinant human Activated Protein C [Drotrecogin alfa (activated)] is recommended in patients at a high risk of death (APACHE II score ≥ 25, or Sepsis-induced multiple organ failure) if there are no contraindications.
- Within 30 days of surgery with the above indications (2C)
- Drotrecogin alfa (activated) is not indicated in adult patients with severe sepsis and lower risk of death. (1A)
- Relative contraindications/warnings should be consider


Drotrecogin Alfa (Activated) In Severe Sepsis: PROWESS Results

- 29% reduction in relative risk of death with Xigris†

PROWESS 28-Day Mortality – High Risk of Death Patients*

- Absolute Risk Reduction = 13%

Mortality Rate

Placebo Drotrecogin alfa (activated)

*as defined by APACHE II ≥25
†relative risk reduction at 28 days
Data on file, Eli Lilly and Company.
See important safety information in this presentation.
What are the Challenges to Appropriate Screening and Administration of Xigris® (drotrecogin alfa [activated])?

- Concerns about risk of bleeding
- Restrictive order set
- Inconsistent screening process
- Cost issues

Safety Profile

- Low incidence of serious bleeding events*
- Rate of serious bleeding events during infusion in high-risk patients:
  - PROWESS: 2.2% (9 of 414) in drotrecogin alfa (activated) patients vs 0.7% (3 of 403) in standard therapy patients
- Rate of ICH in high-risk patients during infusion:
  - PROWESS: 0.2% (1 of 414) in drotrecogin alfa (activated) patients
    - Associated with severe thrombocytopenia (platelet count < 30,000/mm³)
- Not associated with other adverse events

*Serious bleeding events were defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event requiring the administration of ≥ 3 units of packed red blood cells per day for 2 consecutive days, or any bleeding event assessed as a serious adverse event.

†At the time of enrollment in the PROWESS study, the patient had a platelet count above 30,000/mm³. The patient’s platelet count fell to less than 30,000/mm³ after drotrecogin alfa (activated) therapy was initiated.

Data on file, Eli Lilly and Company

See important safety information and full prescribing information in this presentation.
Drotrecogin Alfa (Activated) Has a Favorable Risk/Benefit Profile

8 times more likely to save an additional life than observe an additional serious bleeding event *

* Based on a 13% 28-day survival benefit and a serious bleeding rate during infusion attributable to Xigris of 1.5% (13% ÷ 1.5% = 8.7) in patients with an APACHE II score ≥ 25.

Data on file, Eli Lilly and Company.

CONTRAINdications

Drotrecogin alfa (activated) increases the risk of bleeding. Drotrecogin alfa (activated) is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity.

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

Drotrecogin alfa (activated) is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product.

See full Prescribing Information available at this presentation.
Important Safety Information

WARNINGS

Bleeding

• Bleeding is the most common serious adverse effect associated with drotrecogin alfa (activated) therapy. Each patient being considered for therapy with drotrecogin alfa (activated) should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

• Certain conditions, many of which led to exclusion from the Phase 3 trial, are likely to increase the risk of bleeding with drotrecogin alfa (activated) therapy. For individuals with one or more of the following conditions, the increased risk of bleeding should be carefully considered when deciding whether to use drotrecogin alfa (activated) therapy:
  - Concurrent therapeutic dosing of heparin to treat an active thrombotic or embolic event
  - Platelet count < 30,000 x 10^6/L, even if the platelet count is increased after transfusions
  - Prothrombin time-INR > 3.0
  - Recent (within 6 weeks) gastrointestinal bleeding
  - Recent administration (within 3 days) of thrombolytic therapy
  - Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
  - Recent administration (within 7 days) of aspirin > 650 mg per day or other platelet inhibitors
  - Recent (within 3 months) ischemic stroke
  - Intracranial arteriovenous malformation or aneurysm
  - Known bleeding diathesis
  - Chronic severe hepatic disease
  - Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

See full Prescribing Information available at this presentation.
Additional Management Bundle Components

Low Tidal Volume Ventilation: SSC Recommendations

- Target tidal volumes to < 6 mL/kg (predicted body weight) in patients with ALI/ARDS (1B)
- Initial upper limit goal for plateau pressures in a passively inflated patient be < 30 cm H₂O (1C)
- Hypercapnia can be tolerated in patients with ALI/ARDS if required to minimize plateau pressures and tidal volumes (1C)
- Recommend that positive end expiratory pressure be set as to avoid extensive lung collapse at end-expiration (1C)
- Suggest prone positioning in ARDS patients requiring potentially injurious levels of FiO₂ or plateau pressures in facilities that have experience with the practice (2C)

Corticosteroids In Septic Shock: SSC Recommendations (2C)

- Intravenous corticosteroids should only be given to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy.

- Suggest that the ACTH stimulation test should NOT BE used to identify the subset of adult with septic shock who should receive hydrocortisone. (2B)

- We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available. (2B)
  - Administer intravenous hydrocortisone <300 mg daily (1A)
  - Fludrocortisone is optional if hydrocortisone is used (2C)


Hydrocortisone Therapy for Patients with Septic Shock

- **Design**: Multicenter, randomized, double-blind, placebo-controlled trial

- **Population**: 499 patients with septic shock—BP<90 systolic despite adequate fluid replacement or vasopressors for at least one hour (onset of shock within previous 72 hrs)

- **Method**: 2 groups: one group received 50mg hydrocortisone every 6 hrs for 5 days, then tapered; other group received a placebo.

- **End Point**: 28 day mortality

Sprung, NEJM,2008; Vol 358 No 2
Hydrocortisone Therapy for Patients with Septic Shock--Results

• No significant difference between 2 study groups in rate of death at 28 days (no matter if responded or not to corticotropin)

• Duration of time to reversal of shock was significantly shorter among all pts receiving hydrocortisone (3.3 days vs 5.8 days; p<0.001)

• Pts in this study who has a SBP of< 90mmHg at 1 day after fluid and vasopressor resuscitation had mortality of 56% if received placebo and mortality of 44.9 if received hydrocortisone (difference of 11.4%)—similar to Annane et al results.

• In hydrocortisone group there was an increased incidence of superinfections, including new episodes of septic shock

Sprung, NEJM,2008; Vol 358 No 2

Controversies/Challenges

• Why did patients improve with EGDT
  – Tissue oxygenation target
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    • ScvO2
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Glucose Control: SSC Recommendations

- Initial stabilization of patients with severe sepsis and hyperglycemia who are admitted to the ICU receive IV insulin therapy to reduce blood glucose levels. (1B)

- Use of a validated protocol and target glucose levels to < 150 mg/dL range. (2C)

- All patients receiving IV insulin should receive a glucose calorie source and blood glucose values should be initially assessed every 1-2 hrs, then q 4 hours after stabilization. (1C)

- Low glucose levels obtained by Point of Care testing should be interpreted with caution (1B)


NICE Study

- 6104 Critically Ill Patients within 24 hrs of admission to ICU randomized

- Data evaluated on 3010 pts in intensive control group (target 81-108 mg/dL) & 3012 pts to conventional group (target < 180 mg/dL)

- Similar characteristics at baseline

- Results:
  - Conventional group has significantly lower number of deaths
  - Severe hypoglycemia (blood glucose < 40mg per dL greater in intensive control group (6.8% vs. .5% (p<0.001

What to Do Now?

Continue to Optimize Management of Glucose to Prevent Hyperglycemic & Hypoglycemic Events...range target to < 180 mg/dL, stop infusion at 140 mg/dL

Do NOT Return to Sliding Scale

Sepsis Evidence Implementation

Using the Bundles: Does it Make a Difference?

Surviving Sepsis Campaign

- 252 hospitals in 18 countries
- Data from January 2005-March 2008
- Observational; time series
- Baseline is first quarter data was collected
- Use of standardized screening tool
- Excluded site if less than 20 patients or less than 3 months of results
- Final Sample Size: 15,022 patients from 166 sites (95% of total)
  - North America: 58%
  - Europe: 31%
  - South America: 10%

## Surviving Sepsis Campaign Results

<table>
<thead>
<tr>
<th>Entry Point</th>
<th>Subjects</th>
<th>Mortality (hosp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>52%</td>
<td>27.6</td>
</tr>
<tr>
<td>ICU</td>
<td>12.8%</td>
<td>41.3</td>
</tr>
<tr>
<td>Ward</td>
<td>34.8%</td>
<td>46.8</td>
</tr>
</tbody>
</table>

Hospital mortality went from 37% to 30%
7% ARR; 19% RRR; p< 0.007 when risk adjusted 5.4 % ARR


## Surviving Sepsis Campaign Bundle Compliance

<table>
<thead>
<tr>
<th>Bundle</th>
<th>Baseline</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resuscitation</td>
<td>10.9 %</td>
<td>31.3 %</td>
</tr>
<tr>
<td>Management</td>
<td>18 %</td>
<td>36 %</td>
</tr>
</tbody>
</table>

Hospital Mortality decreased by 5.4%
20 % improvement in compliance with bundles

Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: Results of a three-year follow-up quasi-experimental study

Álvaro Castellanos-Ortigo, MD, PhD; Borja Suberviola, MD; Luis A. García-Artadiño, MD; Marisa I. Soler, MD; Fernando Orfiz, MD; Javier Llanes, MD, PhD; Miguel Delgado-Rodríguez, MD, MPH, PhD

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Critical Care Medicine, 2010;38;1036-1043