ACUTE EXACERBATIONS OF COPD
ROLE OF INFECTION AND ANTIMICROBIAL THERAPY

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On behalf of the IDAB workgroup
ACUTE EXACERBATIONS OF COPD: Overview of topics

1. DEFINITIONS: COPD & AECOPD

2. IMPORTANCE / IMPACT OF AECOPD

3. ETIOLOGY OF AECOPD: non-infectious, infectious

4. DIAGNOSIS OF AECOPD

5. TREATMENT OF AECOPD

6. PREVENTION OF AECOPD
Definition of COPD : GOLD

“Chronic obstructive pulmonary disease (COPD) is a disease state characterized by the progressive development of airflow limitation that is not fully reversible.

The airflow limitation *(defined as an FEV₁/FVC ratio < 70%)* is usually both progressive and the result of an abnormal inflammatory response of the lungs to noxious particles and/or gases *(usually from tobacco smoke)*.

Systemic inflammatory component.
Spirometry: Normal and COPD

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>4.150</td>
<td>5.200</td>
<td>80 %</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>2.350</td>
<td>3.900</td>
<td>60 %</td>
</tr>
</tbody>
</table>

FEV₁: Forced Expiratory Volume in 1 second
FVC: Forced Vital Capacity
FEV₁/FVC: Ratio of FEV₁ to FVC
GOLD classification of COPD severity

Stage 1 - 4: obstructive defect: \( \text{FEV}_1 / \text{FVC} < 70\% \)

- Stage 1: \( \text{FEV}_1 \geq 80\% \) P +/- symptoms
- Stage 2: \( \text{FEV}_1 \geq 50\% \) P +/- symptoms
- Stage 3: \( \text{FEV}_1 \geq 30\% \) P +/- symptoms
- Stage 4: \( \text{FEV}_1 < 30\% \) P or
  \( \text{FEV}_1 < 50\% \) P plus CRIS or RHF
COPD differs from simple CB

• Simple (smoker’s) CB: “chronic cough and sputum production for > 3 mo/yr for > 2 yrs” without airflow limitation

=/=

• COPD: smoker’s lung disease (CB, bronchiolitis, emphysema) leading to airflow obstruction, hence, reduced pulmonary functional reserve
Smoking cessation is the only intervention shown to slow the rate of decline in lung function in COPD.

Definition of AECOPD

- There is no widely agreed and consistently used definition [Pauwels 2004]

- Considerable heterogeneity in presentation (mild to life threatening)

- Differentiate AE from temporary, more progressive worsening of symptoms [Burge 03/21] [Rodriguez-Roisin 00/16]
ERS/ ATS 2004 COPD guideline:

- An AE of COPD is an *(acute)* event in the natural course of the disease characterised by a change in the patient’s baseline *symptoms* (dyspnea, cough and/or sputum) beyond day-to-day variability and sufficiently severe to warrant a change in management.

- Operational classification of severity:
  - Level I: treated at home
  - Level II: requires hospitalisation
  - Level III: leads to respiratory failure
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4. Diagnosis of AECOPD

5. Treatment of AECOPD

6. Prevention of AECOPD
Importance / Impact of AECOPD

- Common and frequent event in many patients
  (median frequency 2.7/y in moderately severe COPD) [Seemungal 98/05]

- Frequency and severity of AE increase with increasing severity of COPD
  [Donaldson 03/19] [Vestbo 89/02], age and bronchial hypersecretion

- Recovery is prolonged and often incomplete in a significant proportion of patients [Seemungal 00/11]

- Important cause of the considerable morbidity and mortality associated with COPD
The clinical course of COPD: consequences of exacerbations

COPD

- Air trapping
- Expiratory flow limitation
- Breathlessness
- Inactivity
- Poor health-related quality of life
- Hyperinflation
- Deconditioning
- COPD exacerbations
- Increased mortality with exacerbation hospitalizations
- Reduced health-related quality of life
- Accelerated decline in FEV₁
- Increased health resource utilization and direct costs

Exacerbations
Effect of LRTI on annual rate of decline of FEV$_1$ (ml/yr)

Kanner RE et al. AJRCCM 2001
Percentage change in FEV₁ over 4 y

Donaldson GC et al. Thorax 2002; 57: 847-852
Impact of AECOPD on COPD’s course

• As yet unaccomplished goals of COPD treatment
  – Slow down decline in PF
  – Prolong survival

• AEsCOPD
  – boost COPD’s already accelerated decline in PF
  – shorten life expectancy

• Reduction in frequency of AECOPD may have a major impact on COPD’s natural course and is a primary goal in the treatment of COPD
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6. PREVENTION OF AECOPD
<table>
<thead>
<tr>
<th>Etiology of acute exacerbations of COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>Bronchial infection (viral, bacterial) in ~ 50-80 %?</td>
</tr>
<tr>
<td>Non-infectious (air pollution, ...)</td>
</tr>
<tr>
<td>Unidentified (1/3)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Rib fractures/chest trauma</td>
</tr>
<tr>
<td>Inappropriate use of sedatives, narcotics, ß-blocking agents</td>
</tr>
<tr>
<td>R- and/or L-heart failure or arrhythmias</td>
</tr>
</tbody>
</table>
Etiology of primary AECOPD

- **80%** infectious
  - Bacterial pathogens
    - 40 - 50%
  - Viral infection
    - 30 - 40%
  - Atypical Bacteria
    - 5 - 10%

- **20%** non-infectious
  - Environmental factors
  - Non-compliance with medications

Sethi et al. Chest 2000; 117: 380s-5s
# Major Bacterial Pathogens in AECOPD

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>% Culture +</th>
<th>Percentage of total isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>H. influenzae</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9614</td>
<td>48.6</td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>687</td>
<td>53.7</td>
<td>31.2</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>140–2180</td>
<td>28.1–88.6</td>
<td>13–50</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>14 studies meta-analysis</td>
<td>Sputum specimens</td>
<td>Non-typeable</td>
</tr>
</tbody>
</table>

Obaji & Sethi. Drugs and Aging 2001; 18: 1-11
Bacterial Pathogens According to Severity of Underlying COPD

Stage I
- FEV₁ 100%P
- S. pneumoniae
- Streptococcus species
- S. aureus

Stage II
- FEV₁ 50%P
- H. influenzae
- M. catarrhalis
- H. parainfluenzae

Stage III
- FEV₁ 35%P
- Enterobacteriaceae
- P. aeruginosa

Stage IV

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4. DIAGNOSIS OF AECOPD: AECOPD is a clinical diagnosis: based on signs & symptoms. There is no confirmatory diagnostic test.

5. TREATMENT OF AECOPD

6. PREVENTION OF AECOPD
ACUTE EXACERBATIONS OF COPD: Overview of topics

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4. DIAGNOSIS OF AECOPD

5. TREATMENT OF AECOPD: general therapy antibiotic therapy

6. PREVENTION OF AECOPD
Earlier recognition and treatment of AE improves recovery [Wilkinson 2004]

1. BRONCHODILATORS (inhaled, via spacer or nebulised)
   - increase dose and / or frequency
   - combination of a fast-acting $\beta_2$-agonist + anticholinergic

2. SYSTEMIC STEROIDS (PO or IV $\rightarrow$ PO)
   - methylprednisolone 0.5 mg/kg/d
   - short (10-14 days) course (cave side effects)

3. SUPPORTIVE MEASURES
   - Controlled oxygen therapy (to obtain an $S_aO_2 > 90\%$)
   - NIPPV (if Acute Ventilatory Failure)
   - No proven effect of physiotherapy, mucolytics (anti-oxidants), theophylline

4. ANTIBIOTICS: controversial
Antibiotics in AECOPD: PROBLEMS:

- In principle, antibiotic treatment is only indicated in bacterial AECOPD
  - Not all AEs are of bacterial origin, hence require antibiotic treatment
  - However, in clinical practice it is difficult/impossible to differentiate a bacterial AE from a non-bacterial (viral or non-infectious) AE: there is no clinical/paraclinical diagnostic marker of a bacterial AE
- Even if a bacterial pathogen is found, there is always the issue of chronic (upper/lower) airway colonisation and/ or innocent bystander
Damaged airway mucosa

Scanning electron micrograph showing bacterial damage to the cilia and epithelium

P K Jeffery
Summary of Pathogenesis

Impaired host defenses:
- Respiratory virus
- New strains of bacteria
- Environmental irritants

Smoking/irritants

Chronic bacterial colonization

Damaged respiratory epithelium

Acute or chronic inflammation
(bacterial + host-mediated inflammatory factors)

Progressive loss of lung function and deteriorating quality of life

Acute cycle

Chronic cycle

Chronic inflammation
(bacterial + host-mediated inflammatory factors)
Bronchoscopy in AECOPD

Monso et al. AJRCCM 1995:1316-20

<table>
<thead>
<tr>
<th>% positive cultures</th>
<th>&gt; 10,000 cfu/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>Exacerbation</td>
</tr>
<tr>
<td>25.0</td>
<td>51.7</td>
</tr>
<tr>
<td>5.0</td>
<td>24.1</td>
</tr>
</tbody>
</table>

$p<0.04$  
$p<0.03$
Lower airway bacterial colonisation in the stable state modulates airway inflammation in COPD

Figure 3  Relationship between total bacterial count (colony forming units/ml) and induced sputum IL-8 levels (Spearman’s rho=0.459, p=0.02). The bacterial count data have been logarithmically transformed.

Interleukin-8 and TNFα during AECOPD: 10-fold increased levels of inflammatory mediators, especially in the presence of bacterial pathogens.
Bacterial eradication reduces and persistence favors airway inflammation following AECOPD

Rising airway bacterial load and species changes are associated with greater airway inflammation and accelerated decline in FEV₁.

- Relationship between FEV₁ decline and change in bacterial load
  - \( r = 0.593, p = 0.001 \)
  - Relationship true for absolute FEV₁ decline and decline expressed as % of baseline FEV₁.

Wilkinson et al. AJRCCM 2003; 167: 1090
Antibiotic Treatment of AECOPD

A) WHEN ANTIBIOTICS?

Criteria usually employed:

- Symptoms/severity of the AE:
  - presence of **3/3 Anthonisen criteria** (i.e. more severe AE, encompassing 40% of all patients with AECOPD) increases the chance that antibiotics are helpful [Anthonisen 87/01]
  - presence of **2/3 Anthonisen criteria if sputum purulence** is one of them
    i.e., purulence likely indicates the presence of bacteria [Stockley 2000]
  - Saint’s meta-analysis confirms small but significant benefit from antibiotics [Saint 95/01]

- Presence of fever, increased CRP
Severity of AECOPD

→ judged by 3 Anthonisen criteria:

- Worsening of dyspnea
- Increased sputum volume
- Increased sputum purulence
Indication for Empiric Antibiotic Therapy in AECOPD

Severity of AECOPD

→ judged by 3 *Anthonisen criteria*:

- Worsening of dyspnea
- Increased sputum volume
- Increased sputum purulence

3/3 → Type 1 or severe AE
2/3 → Type 2 or moderate AE
1/3 → Type 3 or mild AE
Indication for Empiric Antibiotic Therapy in AECOPD

Severity of AECOPD

→ judged by 3 Anthonisen criteria:

- Worsening of dyspnea
- Increased sputum volume
- Increased sputum purulence

3/3 → Type 1 or severe AE
2/3 → Type 2 or moderate AE
1/3 → Type 3 or mild AE

AB indicated/useful in Type 1 or severe AE, and Type 2 or moderate AE if sputum is purulent
Antibiotics Are Beneficial in AECB: a meta-analysis of placebo-controlled trials

Elmes et al, 1957
Berry et al, 1960
Fear and Edwards, 1962
Elmes et al, 1965
Petersen et al, 1967
Pines et al, 1972
Nicotra et al, 1982
Anthonisen et al, 1987
Jorgensen et al, 1992

Overall

Saint S et al. JAMA 1995; 273(12): 957-60
Antibiotics and AECB: when?

Purulence is an indicator of bacterial infection

A) WHEN ANTIBIOTICS (cont)?

Other criteria to take into account?

- Severity of the AE according to other criteria than Anthonisen’s: symptoms/signs of respiratory failure + ABG/$S_aO_2$ (+ PFT ?) [Nouria 01]
Prospective, randomized, double-blind, placebo-controlled study
93 mechanically ventilated COPD patients

**10 days antimicrobial treatment improves outcome of AECOPD**

<table>
<thead>
<tr>
<th></th>
<th>Ofloxacin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>400 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td>4 %</td>
<td>22 %</td>
</tr>
<tr>
<td><strong>Duration of MV</strong></td>
<td>6.4 days</td>
<td>10.6 days</td>
</tr>
<tr>
<td><strong>Duration of hospitalization</strong></td>
<td>14.9 days</td>
<td>24.5 days</td>
</tr>
</tbody>
</table>

Less nosocomial pneumonia
(high failure rate NIPPV, no steroids, infrequent *P. aeruginosa*)

**A) WHEN ANTIBIOTICS (cont)?**

**Other criteria to take into account?**

- Severity of the AE according to Anthonisen’s criteria and symptoms/signs of respiratory failure (ABG/$S_aO_2$) [Nouria 01]

- **Severity of underlying COPD** (GOLD class III or IV) and active smoking [Miravitlles 1999]
  
  In patients with *milder* COPD antibiotics do not accelerate recovery nor reduce recurrence rate [Sachs 95/09]

  Patients with *severe* functional impairment and higher frequency of AE derived the greatest benefit of antibiotic treatment [Allegra 01]
Clinical response to antibiotic treatment and baseline severity of COPD

Retrospective analysis of a prospective, placebo-controlled trial of antibiotic Rx (amoxi/clav):

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Antibiotic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (FEV₁ 33%)</td>
<td>90.2%</td>
<td>30.2%</td>
</tr>
<tr>
<td>II (FEV₁ 54%)</td>
<td>84.8%</td>
<td>59.4%</td>
</tr>
<tr>
<td>III (FEV₁ 72%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ patients with severe functional impairment and higher frequency of AE derived the greatest benefit of antibiotic treatment

Allegra L et al. Pulm Pharmacol Ther 2001; 14: 149-55
# Empiric Antibiotic Therapy in AECOPD

## IDAB Recommendation

<table>
<thead>
<tr>
<th></th>
<th>GOLD I</th>
<th>GOLD II</th>
<th>GOLD III or IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthonisen 3/3</strong></td>
<td>No / ?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Anthonisen 2/3</strong></td>
<td>No / ?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(incl. sputum purulence)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthonisen 1/3</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Acute resp. failure</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**B) WHICH ANTIBIOTICS?**

- **spectrum to include “infernal trio”,** taking into account local susceptibility patterns and policies
- **“newer” drugs** (amoxi-clav, cephalo II, neomacrolides, neofluoroquinolones): less treatment failure and lower relapse rates, but higher costs and possible resistance development issues [Adams 97/06] [Destache 99/08]
## Prevalence of ß-lactam resistance among ‘infernal trio’

<table>
<thead>
<tr>
<th></th>
<th>% of total isolates *</th>
<th>Relative frequency (%)</th>
<th>% ß-lactamase producers</th>
<th>ß-lactam resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td>31.2</td>
<td>52.5</td>
<td>20-25</td>
<td>10.5-13.1</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>14.2</td>
<td>23.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>14</td>
<td>23.6</td>
<td>90-95</td>
<td>21.2-22.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59.4</strong></td>
<td><strong>100</strong></td>
<td></td>
<td><strong>31.7-35.5</strong></td>
</tr>
</tbody>
</table>

* Obaii & Sehti 2001
Association of Antibiotics with Relapse Rates in AECOPD

![Bar chart](chart.png)

Relapse Rate (%)

- Antibiotics: 20%
- No Antibiotics: 35%

$p > 0.001$

Association of Antibiotics with Relapse Rates in AECOPD

Novel outcomes in evaluation of antibiotic treatment for AECOPD

- Clinical response: *rapidity* of resolution of symptoms

- Bacteriologic response: *eradication* of the causative pathogen
  - Reducing colonising bacterial load and airway inflammation
  - Slowing progression of underlying COPD (decline in FEV₁ and HRQoL)

- Decreased likelihood of *recurrence/ relapse*
  - Disease- or Infection-free interval
  - Need for additional antibiotics

The ‘fall & rise’ of bacterial AECOPD

Modifying factors

Bacterial load (CFU/ml)

Time to relapse

Clinical threshold

Time (days)

AE
Start AB therapy
Cure
AB
AB1
AB2
AB3
Cure
Cure
Cure
Stop AB

Time to relapse

Infection free interval in AECB

Infection Free Interval

Hypothesized to:
- Relate to decreased number of colonizing bacteria
- Influence cost of treatment of AECB
- Aid in contrasting antimicrobials in AECB
Empiric antibiotic therapy for AECOPD

IDAB 2007
1. Treatment outside the hospital possible

- amoxicillin-clavulanic acid PO
  875/125 mg TID *or* 2000/125 mg BID

- moxifloxacin PO 400 mg OD
  if β-lactam allergy or intolerance

- cycling between amoxicillin-clavulanic acid and moxifloxacin if frequent AECOPD (i.e., ≥ 3 in the previous year)
2. In-hospital treatment necessary

Mild or moderate COPD: GOLD stage I or II (i.e., FEV$_1$ > 50 %P)

- oral treatment possible: same therapy as under 1.

- IV treatment necessary:
  - amoxicillin-clavulanic acid 1g QID
  - moxifloxacin 400 mg OD
  if β-lactam allergy or intolerance
  - sequential IV>PO therapy ASAP within the same drug class

- cycling between amoxicillin-clavulanic acid and moxifloxacin
  if frequent AECOPD (i.e., ≥ 3 in the previous year)
3. In-hospital treatment necessary
Severe or very severe COPD: GOLD stage III or IV (i.e., FEV$_1$ < 50 %P)
No risk factors for *Pseudomonas aeruginosa*

- *amoxicillin-clavulanic acid IV 1g QID*
- *moxifloxacin PO 400 mg OD if intact GI function*
- *moxifloxacin PO or IV 400 mg OD if β-lactam allergy or intolerance*
- *sequential IV>PO therapy ASAP within the same drug class*
- *cycling between amoxicillin-clavulanic acid and moxifloxacin if frequent AECOPD (i.e., ≥ 3 in the previous year)*
4. In-hospital treatment necessary
Severe or very severe COPD: GOLD stage III or IV (i.e., \( \text{FEV}_1 < 50 \% \text{P} \))
With risk factors for *Pseudomonas aeruginosa*

- recent hospitalization
- frequent administration of antibiotics (>4 courses in last year)
- recent administration of antibiotics (last 3 months)
- very severe COPD (Stage IV)
- isolation of *P. aeruginosa* during previous AECOPD
- colonization with *P. aeruginosa* during stable period
- presence of bronchiectasis
4. In-hospital treatment necessary
Severe or very severe COPD: GOLD stage III or IV (i.e., FEV₁ < 50 %P)
With risk factors for *Pseudomonas aeruginosa*

- if oral therapy possible: ciprofloxacin PO 750 mg BID

- if IV treatment necessary:
  - anti-*Pseudomonas* β-lactam:
    - ceftazidime 2 g TID
    - cefepime 2 g TID
    - piperacillin-tazobactam 4 g QID
  - ciprofloxacin 400 mg TID

- add IV aminoglycoside active against *Pseudomonas aeruginosa* if
  - instability on the hospital ward
  - requirement for ICU admission
Thank you for your attention

On behalf of the
IDAB WORKGROUP AECOPD

Herman Goossens
Paul Jordens
Willy Peetermans
Yves Sibille
Yvan Valcke
Pascal Van Bleyenbergh
Jan Vandevoorde
Johan Van Eldere
Yves Van Laethem
Walter Vincken (coordinator)

And the plenary IDAB presided by Dirk Vogelaers
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Prevention of AECOPD

- Smoking cessation
  Only intervention with proven effect on mortality
- Regular maintenance treatment [GOLD guideline]
  especially tiotropium, LABA, iGCS (in GOLD class 3 or 4), NAC\(^{(4)}\), rehabilitation
- Vaccination (influenza, S. pneumoniae)
- Prevention of infection (viral, bacterial) \(^{(1)}\) : AB associated with lower relapse rates \(^{(2)}\)
- Immunostimulating agents \(^{(3)}\)

\(^{(2)}\) Adams et al. Chest 2000;17:1345-52
\(^{(3)}\) Collet et al. Can Respir J 2001;8:27-33; Collet et al. AJRCCM 1997;156:1719-24
\(^{(4)}\) [Stey 2000]
### Indications for hospital assessment or admission for acute exacerbations of COPD

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Onset of new physical signs (e.g., cyanosis, peripheral edema, newly occurring arrhythmias)
- Failure of exacerbation to respond to initial medical management
- Severe background COPD and patients on LTOT
- History of frequent AE and hospitalizations (>3 in the past year)
- Chronic oral steroid use
- Significant comorbidities
- Older age
- Poor or deteriorating general condition with little activity
- Insufficient home support
- Diagnostic uncertainty

GOLD 2002
Indications for ICU admission of patients with acute exacerbations of COPD

- Severe dyspnea that responds inadequately to initial emergency therapy
- Persistent or worsening hypoxemia ($P_aO_2 < 50 \text{ mmHg}$), and/or severe/worsening hypercapnia ($P_aCO_2 > 70 \text{ mmHg}$), and/or severe/worsening respiratory acidosis ($\text{pH} < 7.30$) despite supplemental oxygen and NIPPV
- Presence of other end-organ dysfunction
- Confusion, lethargy, coma
- Hemodynamic instability