How We Organise Clinical Investigations
Five Year Experience of Chinese Collaborative Study Groups for Neonatal/Pediatric Respiratory Failure

Bo Sun, Liling Qian, Wenliang Yu
Children’s Hospital of Fudan University
Geneva 2006-06 WPCC8
Current Situation of Pediatric Intensive Care in China

- **National University, Pediatric Centers**
  - **Settings**: PICU, NICU, P/NICU
  - **Function**: National programmes of clinical investigation and CME, serve 10+ millions population

- **Provincial Women and Children’s Health Centers**
  - **Settings**: Children’s Hosp-PICU, NICU; Maternity-NICU
  - **Function**: Regional CME and clin investig, 5-10 mln

- **Prefectural/Sub-province Medical Centers**
  - **Settings**: NICU+P
  - **Function**: Service and clin investig, 1-5 mln
Location of the member centers
Background

Experience (50-70’s) → Evidence -based Medicine (80-90’s)

Collaboration → Internet

Network-based 90’s-current

Multicenter RCT
Current Situation of Pediatric Intensive Care in China

Advantage: sufficient cases

Experience  → evidence-based medicine
Few multicenter clinical study

challenge

- Limited funds
- Change old mode
- Establish network

network
Objectives

Descriptive clinical epidemiology
- Profile of respiratory failure
- Resource allocation
- Quality improvement

Interventional RCT study
- Ethics and cultural/social
- Guidelines
- Nursing care

Network
Group’s network

Collaborative Study Group

Management Supervision

Clinical Center Data Collection

Submission

Electronic Data

Feedback

Collaborative Center Data Processing

Monthly Report
Patient Information

Case report form:
- Demographic characteristics
- Medical history, health status, family, et al
- Disease components
- SNAPPE-II or PIM
- Intervention, et al
- Outcome and burden, et al

Monthly report form:
- New admission according to inclusion and exclusion criteria, et al
Man power input

Clinic directors:
- Commitment to the agreement
- Staffs and funds
- Responsible to all the cases and report forms
- Contact person
- Manuscript co-authorship

Key staffs:
- Daily collection of the case information
- Reporting to the collaborative center
- Responsible for data uploading and inquiry
Staff training

At the start period:
- Courses to study protocol and case reporting forms
- Practice communication

During the study period:
- Telephone communications
- Newsletters
- Attending workshops

At the conclusion:
- Assessment of unit performance
Part I

Prospective, Multicenter Clinical Survey of Neonatal Acute Respiratory Failure in 23 Neonatal Intensive Care Unit in China

Chinese Collaborative Study Group for Neonatal Respiratory Diseases
2004-2005
Background

- Half of the mortality of children below 5 years old is in neonatal period
- NRF is a main cause of death with high mortality, morbidity and costs
- Epidemiological data are lacking but essential for promoting intensive care quality and health policy
## Background

ARF surveys (mainly retrospective)

<table>
<thead>
<tr>
<th>Author</th>
<th>country</th>
<th>time</th>
<th>object</th>
<th>Incidence(%)</th>
<th>Mortality(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonafe</td>
<td>Italy</td>
<td>1996</td>
<td>population</td>
<td>3.3</td>
<td>14.8</td>
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<td>Rubaltelli</td>
<td>Italy</td>
<td>1998</td>
<td>population</td>
<td>2.2</td>
<td>14.6</td>
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<tr>
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<td>USA</td>
<td>2001</td>
<td>population</td>
<td>1.8</td>
<td>11.1</td>
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<tr>
<td>Ali</td>
<td>Tobago</td>
<td>2003</td>
<td>population</td>
<td>1.4</td>
<td>33.0</td>
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<tr>
<td>Lee</td>
<td>Canada</td>
<td>2000</td>
<td>NICU</td>
<td>43</td>
<td>/</td>
</tr>
</tbody>
</table>

- Variable results were due to the differences in population, inclusion criteria and geography
Background

- Lack of epidemiological data of ARF in China
- A survey based on population is difficult — no reliable birth registration for vital statistics
- A survey based on clinical record is feasible — relatively easier with admission registries, etc…
Method

Prospective multicenter

Period

2004.3-2005.2

Inclusion Criteria

1. All NICU admission
2. NRF: defined as requiring MV or nasal CPAP

Objectives

1. Incidence, mortality
2. Risk factors
3. Underlying diseases
Data Submission & Communication

Network website
www.shlung.com/neonet
Results
(2004.3.1 ~ 2005.2.28)

Nicu 13038

Nrf 1863

159

438

Incidence: 14.3%

Mortality: 32.0%

Death 8.5%

Give up 23.5%
Gestational Age Distribution of NRF

34.9± 4.1 w

63.3% preterm
Birth Weight Distribution of NRF

2309± 832 g

59.8% LBW
Clinical features

Sex M/F = 3 : 1

- Male: 75.5%
- Female: 24.5%
**Clinical features**

**SGA**

- **LGA**: 3.8%
- **SGA**: 17.2%
- **NGA**: 79.0%

**Bar chart**

- <28
- 28-32
- 33-37
- 38-42
- >42

%-axis: 0, 5, 10, 15, 20, 25

**GA (w)**
Clinical features

Congenital Malformation (8.5%)

- CHD 62.0%
- GI 10.1%
- resp 14.7%
- others 13.2%

**Graph:**
- Y-axis: congenital reform (%)
- X-axis: GA (w)
  - <28
  - 28-32
  - 33-37
  - 38-42
  - >42
**Antenatal Steroids**

**Risk factors**

GA = 34 w

- No: 68.9%
- Partial: 16.8%
- Completed: 14.3%
**Risk factors**

**Delivery Mode**

- SVD: 52.2%
- Forceps: 4.5%
- Selective C/S: 21.9%
- Emergency C/S: 21.4%

Bar chart showing:
- <28 weeks: 15%
- 28-32 weeks: 30%
- 33-37 weeks: 55%
- 38-42 weeks: 45%
- >42 weeks: 60%
Risk factors

Multiple Birth

- Singletons: 87.1%
- Twins: 11.6%
- Triplets: 1.0%
- Quadruplets: 0.3%
Risk factors

5 min Apgar <7

- 21.0% <7
- 79.0% = 7

5' Apgar < 7 (%)

<table>
<thead>
<tr>
<th>GA (w)</th>
<th>&lt;28</th>
<th>28-32</th>
<th>33-37</th>
<th>38-42</th>
<th>&gt;42</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>30</td>
<td>15</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>
Risk factors

Maternal Diseases

Age: 27.8 ± 4.8 yrs, Median: 27.0 (19-51) yrs

Incidence (%) of risk factors:
- Pregnant hypertension: 7.5%
- Placenta previa: 5.3%
- PPRM: 4.9%
- Diabetes: 1.6%
Primary Causes of Assisted Ventilation

- PI after delivery: 6.3%
- Sepsis: 2.3%
- Apnea of prematurity: 4.1%
- HIE: 5.6%
- TT: 7.0%
- Aspiration of amniotic fluid: 8.6%
- MAS: 8.7%
- PI before or during delivery: 13.9%
- Others: 11.1%
- RDS: 32.3%
Critical scores

SNAPPE-II (Median 20)

Critical scores

SNAPPE-II

Critical scores
Critical scores

SNAPPE-II and Mortality

Diagram showing the relationship between SNAPPE-II scores and mortality. The x-axis represents SNAPPE-II scores, while the y-axis shows the number of infants in each score category. Mortality is represented as a percentage on the right y-axis, increasing with higher SNAPPE-II scores.
Respiratory Therapy

Duration of intervention: $91 \pm 94$ h, Median: 70 h

GA (weeks)

- <33
- 33-36.9
- $\geq 37$

Legend:
- nCPAP
- both
- Vent
Surfactant and INO Therapy

NRF: 1863

- Surfactant
  - GA: 31.8 ± 3.2 w
  - BW: 1743 ± 637 g

- iNO

- 15.6%

Prophylactic surfactant:

- BW < 1200g: 14.4%
- GA < 30 w: 9.5%

RDS: 602

- 36.0%
NICU Stay (Median 8 days)

<table>
<thead>
<tr>
<th>GA (w)</th>
<th>Length of NICU Stay (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>34</td>
</tr>
<tr>
<td>28-32</td>
<td>11</td>
</tr>
<tr>
<td>33-37</td>
<td>8</td>
</tr>
<tr>
<td>38-42</td>
<td>7</td>
</tr>
<tr>
<td>&gt;42</td>
<td>8</td>
</tr>
</tbody>
</table>

N = 18, 280, 333, 289, 7
NICU Cost (Median 8315 Chinese Yuan)
Mortality Among Hospitals

Western Areas: 36.0 % vs. Eastern Areas: 29.2 % (p=0.002)
Cost Among Hospitals

- **Western Areas**: 6274
- **Eastern Areas**: 9128 (p=0.000)
CONCLUSIONS

- **First** multicenter prospective study of NRF in China
  - Overall reflects the incidence, disease components and critical care levels
  - Find out differences when compare with other countries for improvement national and regional intensive care

- **First** multicenter neonatal network based on advanced concepts of international standards, enabling cost-effectiveness and interventional investigation
Part II

Prospective, Multicenter Clinical Survey of Acute Respiratory Distress Syndrome in 25 Pediatric Intensive Care Unit in China

Chinese Collaborative Study Group for Acute Respiratory Distress Syndrome
Participants (25 PICUs)
Method

Inclusion Criteria

All PICU Admissions (29 d-14 y)

ARDS

Prospective Multicenter

Period

2004.1-2005.6

Total 12mon

Objectives

Incidence, mortality, risk factors

Disease Processing

Differences between PICUs
All PICU Admissions → Critical Ill → ARDS → Mortality

PCIS

AECC 1994

Treatment Protocol
Acute PaO$_2$/FiO$_2$ < 7 days

PaO$_2$/FiO$_2$ Oximeter Ventilator

Chest X-ray Confirmed by 2 Radiologists

Cardiogenic? Echocardiograph
ARDS Final Workshop
(2005.06.16)
2004.1 ~ 2005.6 (25 PICUs)

PICU 12018

Critically ill 7269

Respir failure 2009

Mechan vent 1957

ARDS 105

ARDS Death 64

ARDS

Incidence: 1.44% (105/7269)
Mortality: 61.0% (64/105)
Monthly distribution of the cases

\[ \chi^2 = 5.867, \quad P = 0.862 \]
Pneumonia 55%
Asphyxia 3%
Others 11%
Cardiopulmonary Bypass 3%
Sepsis 23%
Poison 5%
# Preliminary Diseases

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Cases/Death (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrapulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62/36</td>
</tr>
<tr>
<td>TB</td>
<td>58/35</td>
</tr>
<tr>
<td>Contusion</td>
<td>1/0</td>
</tr>
<tr>
<td>Near-drown</td>
<td>2/1</td>
</tr>
<tr>
<td><strong>Extrapulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>43/28</td>
</tr>
<tr>
<td>Toxication</td>
<td>24/19</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>5/2</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>3/2</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>2/1</td>
</tr>
<tr>
<td>Conjunctive tissue diseases</td>
<td>2/2</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>3/0</td>
</tr>
<tr>
<td>Trauma</td>
<td>2/0</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>105/96</strong></td>
</tr>
</tbody>
</table>
### Incidence and Mortality in Pneumonia and Sepsis Induced ARDS

<table>
<thead>
<tr>
<th></th>
<th>Pneumonia</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PICU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>3013</td>
<td>688</td>
</tr>
<tr>
<td>Death</td>
<td>159</td>
<td>122</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>5.3 (4.5, 6.1)*</td>
<td>17.7 (14.9, 20.8)</td>
</tr>
<tr>
<td><strong>ARDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>Incidence(%)</td>
<td>1.9 (1.5, 2.5)</td>
<td>3.5 (2.2, 5.1)</td>
</tr>
<tr>
<td>Death</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>60.3 (46.6, 73.0)</td>
<td>79.2 (57.8, 92.9)</td>
</tr>
</tbody>
</table>

*95% CI
Age Distribution

![Age Distribution Chart](chart.png)

- New Cases are distributed across various age groups.
- The highest number of new cases is observed in the age group 1.
- A statistical test shows a significant difference, with $P < 0.001$.
Onset of ARDS

- Time interval from preliminary disease to onset of ARDS: 
  75.6± 53.0 h
- 25th, 50th, 75th, 90th, 95th percentile: 24, 72, 120, 144, 168 h
- ARDS death within 24hrs/ total ARDS death =37.7% (23/61)
The mortality of ARDS in China is significantly higher than those in developed country (30-40\%).

The burden of ARDS is heavy.
Mortality of ARDS in different PICUs

Mortality (%)
Mortality of ARDS on MV in different PICUs

![Graph showing mortality and patients on MV in different PICUs.](image-url)
Lung Mechanism
Pressure

Days after onset of ARDS

PIP (cmH2O)

PEEP (cmH2O)

MAP (cmH2O)

death
Survivor

? /\_\_\_\_\_\_, P<0.05
? /\_\_\_\_\_\_, P<0.01
Lung Mechanism

Volume

Cdyn (l/min)

Vte (ml/kg)

MV (l/min)

Days after onset of ARDS

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

Days after onset of ARDS

Death

Survivor

? / ̃, P<0.05

? / ̃, P<0.01
Gas Exchange
Blood Gas

PaCO₂ (mmHg)

Days after onset of ARDS

PaO₂ (mmHg)

Days after onset of ARDS

pH

Days after onset of ARDS

death
Survivor

? / | , P<0.05

? / | , P<0.01
## Multi-organ Failure

<table>
<thead>
<tr>
<th>Number</th>
<th>Cases/Death</th>
<th>Mortality(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 2 organs</td>
<td>55/37</td>
<td>67.3</td>
</tr>
<tr>
<td>= 2 EPO*</td>
<td>35/26</td>
<td>74.3</td>
</tr>
<tr>
<td>2 EPO</td>
<td>14/12</td>
<td>84.7</td>
</tr>
<tr>
<td>3 EPO</td>
<td>6/3</td>
<td>50</td>
</tr>
<tr>
<td>4 EPO</td>
<td>10/6</td>
<td>60</td>
</tr>
<tr>
<td>5 EPO</td>
<td>5/5</td>
<td>100</td>
</tr>
</tbody>
</table>

*EPO: extra pulmonary organs
Survival Analysis

Cumulated Survival

Days after onset of ARDS

Cumulated Survival

Death to onset of ARDS (days)

Others
Pneumonia
Sepsis

? : ??????????? 48?
Univariate Logistic Regression Analysis of Risk Factors (34)

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>3.040</td>
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</tr>
<tr>
<td>MOF</td>
<td>3.771</td>
<td>0.011</td>
</tr>
<tr>
<td>Infiltrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 quadrants</td>
<td>0.264</td>
<td>0.002</td>
</tr>
<tr>
<td>3 quadrants</td>
<td>1.494</td>
<td>0.487</td>
</tr>
<tr>
<td>4 quadrants</td>
<td>2.533</td>
<td>0.023</td>
</tr>
<tr>
<td>PCIS (domestic)</td>
<td>0.891</td>
<td>0.001</td>
</tr>
<tr>
<td>pH</td>
<td>0.017</td>
<td>0.020</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>1.026</td>
<td>0.049</td>
</tr>
<tr>
<td>OI</td>
<td>1.040</td>
<td>0.116</td>
</tr>
</tbody>
</table>


## Multivariate Logistic Regression Analysis of Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrations</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>2 quadrants</td>
<td>0.175</td>
<td>0.001</td>
</tr>
<tr>
<td>4 quadrants</td>
<td>0.642</td>
<td>0.530</td>
</tr>
<tr>
<td>PCIS (domestic)</td>
<td>0.881</td>
<td>0.001</td>
</tr>
<tr>
<td>PaCO$_2$</td>
<td>1.031</td>
<td>0.030</td>
</tr>
</tbody>
</table>

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Conclusions

- The incidence and mortality of ARDS is 1.44% and 61.0% respectively in PICUs. The mortality of ARDS is 9 folds as those of critically ill patients and is twice that in the developed countries.

- Hospital stay days in ARDS took up 3% of total PICU occupancy and 5.2% of total ICU cost.

- Relatively low critical care level and inhomogeneity in using lung protective strategies are main issues associated with the high mortality.
Future

- How to set up a standardized network
- How to make well use of Chinese clinical resources
- How to improve the critical care in China
Acknowledgement:
Drs. Liling Qian and Wenliang Yu, and Chinese Collaborative Study Group Investigators

Thank you