Protocols: The Good, the Bad and the Ugly

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Protocolized care has been espoused by many as the answer to the problem of variability in medical treatment. The gradual movement in this country towards embracing the concept of evidence-based medicine has given further weight to the notion of rendering care more uniform. By identifying its role as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients,” the proponents of evidence-based medicine seek to meld the competing priorities of physician autonomy and medical accountability. In this presentation, I will examine the impact of protocolized care, particularly as it applies to critical care, on our current practice, looking at the successes and failures of its application. I will then explore the relationship between physicians and protocols, not only in the trenches, but as an extension of the sociologic concept of the relationship between humans and plans in general.

Protocols are specifics plans for care of patients suffering from like conditions. They are related to such other tools as practice guidelines, practice standards, clinical pathways and consensus statements. Generally speaking they specify therapeutic and diagnostic choices that apply to the given condition. Depending on the definition of protocol one utilizes, there are literally hundreds described in the medical literature, with their number ever increasing. Examples that have achieved widely notarized success in the critical care arena include protocols to dictate care in weaning from mechanical ventilation, intensive insulin therapy, transfusion practices, and prevention of ventilator-associated pneumonia. History shows that protocols may be shown to improve outcomes or control costs, but also that some protocols need to be revised or even discarded as time and medical knowledge progress. Other protocols fail to achieve their goals of improved patient outcomes or cost control altogether. I would like to explore the whole relationship between health care providers and protocols in a framework that identifies the keys to successful protocols (Good Protocol, Good Adherence, Desired Effect) with those that are not successful (Good Protocol, Poor Adherance, No Desired Effect) or (Bad Protocol, Good Adherence, No Desired Effect). I will assume it to be self-evident that the fourth permutation (Bad Protocol, Poor Adherence, No Desired Effect), while it may be a commonplace experience, does not warrant further discussion. The key questions here are: What constitutes a Good Protocol? and What are the barriers to protocol adherence?

As an illustration I would like to look at the example of protocolized weaning from mechanical ventilation (MV), seen through the lens of our own noble institution. In 1991, the paper of Yang and Tobin introduced the rapid shallow breathing index (RSBI) to the weaning “vocabulary”. It was touted as the measurement that best predicted successful extubation in patients weaning from MV. It was not surprisingly incorporated into many practitioners’ routine in assessing the weaning status of their patients. In 1996, Ely et al published the landmark article suggesting that once-daily, protocolized screening done by non-physicians led to a shorter duration of MV when compared to usual physician-directed care. Patients who had a PaO2/FiO2 ratio of >200,
were on ≤ 5 cm H2O of PEEP, had adequate “cough” on suctioning, were off sedatives and vasopressors (except that dopamine 5 mcg/kg/min was tolerated – more on this later) and had a RSBI of < 105 were advanced to a two hour trial of spontaneous breathing (SBT). Patients who successfully breathed spontaneously for 2 hours were placed back on the ventilator and the outcome of the trial was relayed to the attending physician. Patients in the control group had the same screening, but were not automatically advanced to the SBT. Median duration of MV was 4.5 days in the intervention arm compared with 6 days in the control arm. Two subsequent confirmatory trials followed in 1999<sup>iii</sup> and 2000<sup>iv</sup>, and in our own institution a major effort was undertaken to export a weaning protocol to all of the ICUs hospital-wide. As implementation began to gain traction and acceptance, the pendulum of the literature began its inexorable reversal of motion. In 2004, Krishnan et al<sup>v</sup> published a study showing no benefit to adding protocol-directed weaning “in a closed ICU with generous physician staffing and structured rounds”, a description closely matching several of the ICU environments in which we were attempting to operationalize such a protocol. Tanios et al<sup>vi</sup> then published the final lethal dagger in the protocol’s heart in 2006, in which they demonstrated that using the RSBI as a weaning predictor actually prolonged weaning time. We found ourselves faced with supporting a protocol that now appeared to be potentially harmful to patients!

This example illustrates several points. The first is that when use of a protocol appears to have a favorable outcome effect on patients, not every component of the protocol may be important in achieving the effect. Here, one can speculate that use of the RSBI as a screening tool may not have contributed to the success of the earlier studies. Second is the issue of protocol adherence. Physicians are notoriously poor at adhering to prescribed practices, be it specific protocols or practice guidelines. Much of the success of the weaning protocols appear to have come from respiratory therapists and nurses being freed to work in parallel with physicians rather than entirely under physicians’ direction. When Finally, what are the attributes of a good protocol? Writing such algorithms generally requires the consensus of several to many clinicians, as well as buy-in from institutional review boards. This is good in that it tempers individual hegemony, but has the limitation that it often forces compromise; one can imagine that including patients still on up to 5mcg/kg/min of dopamine in the original protocol may have been necessary to placate a strident minority. Interestingly, when asked for her intensive insulin therapy protocol, Dr. Van den Bergh replied that she could provide it, but it did not reflect what really happened at the bedside. The nurses in her ICUs considered the protocol to be a starting point or loose guideline, but actually modified the insulin dosing according to their experience and the patients’ responses. Perhaps a truly good protocol is more descriptive than prescriptive, whether for physicians, nurses, or allied providers.

I would like to turn the discussion towards the broader perspective of protocols and practice guidelines seen against the backdrop of the societal framework. The last several decades have been characterized by a movement from an era of unfettered physician autonomy to an era of increasing accountability. This shift can be almost entirely explained as a product of a loss of public trust in the medical profession. In his essay on the subject of practice guidelines, Timmermans<sup>x</sup> invokes the “theory of countervailing powers”, referring to the power of the medical profession to wield control over the technical and formal content of their work, opposed by the power of government to demand accountability and quality optimization from the medical profession. The current climate includes not only incentives to follow certain “best practices”
(pay-for-performance), but a recent governmental decree that it will no longer pay for “preventable complications” occurring during hospitalization (financial punishment). It is not inconceivable to anticipate that physicians and hospitals will be expected to demonstrate adherence to guidelines and protocols to avoid financial repercussions. It is unlikely we can expect a return to increasing autonomy and decreasing accountability in the future. If we accept this premise, then it must be with the greatest care that we craft guidelines and protocols. In this regard, I sense great danger in protocolized care. Failure to adhere to protocols will risk be viewed externally as failing to employ or execute best practices.

In the jargon of sociologists, plans (protocols) constitute an initial “skills-based” approach to performing a task or action. When plans fail, individuals resort to “rules-based” internal functioning that may deviate from the plans, no matter how completely they had previously been thought out. This is considered to be a fundamental aspect of human behavior, and I believe must be applied to achieve “good” protocols. In practical terms, protocols must have intrinsic flexibility such that they guide care but can accommodate deviation and obstacles. Only in this way can they properly match the fundamental behavior of caregivers at the bedside; further, when subjected to external scrutiny, adherence will be easier to demonstrate.

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Prognosis Scores: Better Care?

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ICU Scoring Systems: Better Care?
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Department of Anesthesiology
University of Michigan

Comparison of Citations for Leading Clinical and Scoring System Manuscripts

Factors affecting standardized Mortality ratios
• Health care system characteristics
• Population characteristics
• ICU patterns of care
• Intrinsic deficiencies of the model
• Inconsistent application of the model
• Size of the study population
• Variation in ICU quality of care
• Variation in Hospital Quality of Care

Types of ICU Scoring Systems
• General ICU Outcome Models
  – Case-mix, physiological
    • APACHE; Acute Physiology, Age, Chronic Health Evaluation
    – APACHE II, APACHE III
    • SAPS; Simplified Acute Physiology Score
  – MPM; Mortality Probability Model
  – TRIOS (3-day Recalibrated ICU Outcome Score)
  – PRISM; Pediatric Risk of Mortality
  – PIM II; Pediatric Index of Mortality
  – DDRA; Dynamic Objective Risk Assessment

• Organ system failure
  – MODS; Multiple Organ Dysfunction Score
  – LOGO; Logistic Organ Dysfunction Score
  – GOSSA; Sequential Organ Failure Score
  – SOFA; Sequential Organ Failure Assessment

• Therapeutic Intervention scoring
  – TISS; Therapeutic Intervention Scoring System
    – TISS-28; Simplified
    – NTISS; Neonatal Therapeutic Intervention Scoring

• Surgical & Disease Specific ICU Scores
  – General surgery
    – APACHE, APACHE II, III
    – POSSUM; Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity
    – NSQIP; National Surgery Quality Improvement Program

  – Trauma
    – ISS; Injury Severity Score
    – RTS; Revised Trauma Score
    – TRISS; Trauma Injury Severity Score
  – ASCOT; A severity characterization of Trauma
  – 24h-ICU Trauma Score
  – Pediatric Trauma Score

  – Cardiac/Thoracic Surgery
    – ATS; American Thoracic Society
    – Parsonnet
    – EUROSCORE
    – System 97 score; cardiac surgery
    – QMMI; coronary surgery
    – IRISS; graft failure after lung Tx.
    – Lung Resection Score; thoracic surgery

  – Neuro
    – GCS
    – RASS, RAMsay, CAM-ICU

  – Respiratory/Pulmonary
    – Respiratory Failure Score

  – Renal
    – Dye Induced Renal Failure
    – RIFLE Score; ARF

  – GI/Hepatic
    – Child-Turcotte-Pugh
    – MELD

  – Sepsis
    – PIRo

  – Disease Specific
    – Cancer
      – Chemotherapy, Radiation Therapy
    – Eye induced visual failure
    – SFUO Score; AIDS
    – GNFAPIC
    – Rasmussen
    – Multifocal Lacunar
    – MELD
    – SEPIC

Manuscripts Focusing on ICU Scoring Systems, Prognostic & Outcome Models

Comparison of Citations for Leading Clinical and Scoring System Manuscripts

Types of ICU Scoring Systems

Factors affecting standardized Mortality ratios

1
**Statistics for ICU Scoring Systems**

- **Logistic Regression**
  - $y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p + \varepsilon$
  - $\text{prob} = \frac{e^y}{1 + e^y}$

- **Discrimination**
  - how the model distinguishes the who die from those who live based on estimated probabilities of mortality
  - 0.5 to 1

- **Calibration**
  - observed to predicted outcomes across deciles of mortality risk
  - Hosmer-Lemeshow test (C-statistic)
    - want the P value to be >.05

**Updated Models: APACHE IV, SAPs III, MPM**

- **131,618 ICU admissions**
- **104 ICUs in 45 Hospitals**
- **1-2002 through 12-2003**
- **Newer Data added;**
  - APACHE III APS score
  - Length of stay before ICU admission
  - ICU admit source; floor, ED, OR, direct admit, other ICU, other hospital
  - Unable to assess GCS
  - Pa02/Fi02 ratio
  - Receiving mechanical ventilation
  - MI rec’ing thrombolytics

- **16,784 patients**
- **303 ICUS**
- **10-2002 to 12-2002**

- **3. Pre-ICU Characteristics;**
  - Age, Co-morbidities, vasoactive drugs, intra-hospital location prior to ICU admit, LOS prior to hosp admit.

- **2. Reasons for ICU Admission;**
  - planned/unplanned ICU admit, surgical status, anatomic site of surgery, infection and place acquired prior to hosp admit.

- **3. Physiologic derangement at ICU admission;**
  - GCS, HR, SBP, Bili, temp, creat, WBC, Plts, pH, Vent support and oxygenation.

**Project IMPACT database**

- **124,885 patients**
- **135 ICU’s**
- **98 Hospitals**
- **10-2001 to 3-2004**

**Organ Failure Scores; SOFA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp. PaO2/FIO2</td>
<td>&gt;400</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Resp. Platelets</td>
<td>&gt;150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver/ALT/AST</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt;12</td>
</tr>
<tr>
<td>CV, Hypotension</td>
<td>None</td>
<td>MRA &lt;70</td>
<td>Dop =/Dob or Dap &gt;70</td>
<td>MRA &gt;70 or Dap &gt;70</td>
<td>MRA &gt;70 or Dap &gt;70</td>
</tr>
<tr>
<td>CNS, GCS</td>
<td>15</td>
<td>13, 14</td>
<td>10-12</td>
<td>5-9</td>
<td>0</td>
</tr>
<tr>
<td>Renal, Creat or UO</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9</td>
<td>&gt;5.0 or &gt;800</td>
</tr>
</tbody>
</table>

**Castella, X, CCM 1995**
Organ Failure Scores; SOFA

Scores and Clinical Care: Physiologic vs Organ Failure

Clinician vs. Computer Predictions

Influence of Clinician’s prediction and the final outcome
Scores and End of Life Care; PIC

Identifying Potentially Ineffective Care in the Sicker Critically Ill Patients on the Third ICU Day

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>88%</td>
<td>87%</td>
</tr>
<tr>
<td>Actual</td>
<td>61%</td>
</tr>
</tbody>
</table>

Day 3 aps> day 1 aps in 34/302 = 11%
32/34 patients died, and only 1 survived >100 days.
Sens= 15%, Specificity= 99% (64 to 99.8% CI)
PPV= 97%, 85% to 99.5%
NPV= 31%, 26 to 38%

Scores and End of Life Care; SUPPORT

- 9105 Adults hospitalized with 1 of 9 ‘life-threatening’ diagnoses
- Phase I 4301 patients in prospective observational phase
- Phase II 4804 divided into:
  - MD’s rec’d daily 6-month mort estimates, outcome of CPR & functional disability at 2 months
  - Study nurse facilitated Pt’s preferences and communicated with MDs
- Overall Mort= 47% at 6 months

Results of the SUPPORT Trial

- Phase I:
  - 47% of MD’s aware of Pt’s wishes to avoid CPR
  - 46% of DNRs written within 48 hrs of death
  - 38% of patients that died spent >10 days in the ICU
  - 50% of conscious patients who died reported to be in pain at least half of their admission
- Phase II:
  - No change in intervention group compared to control group
  - Discussion of CPR wishes
  - Incidence or timing of written DNR orders
  - Physician’s knowledge of pt’s wishes not to be resuscitated
  - Days spent in ICU receiving mechanical ventilation or coma before death
  - Level of reported pain
  - Resources used
- Objective measures and/or enhancing opportunities for communication are inadequate to change established practices!

Scores and Benchmarking: CHQC

Do Reports of ICU Scores modify outcomes over time: CHQC

P = .09
Reaction to Poor Performance; CHQC
“Operation That Rated Hospitals Was Success, But the Patient Died”

“The Cleveland Clinic Found Fault with Program of CEOs, Whose Ardor Faded Too.”

Lead-Time Bias in ICU Models

Value of ICU Scoring Systems

- ICU Administrative resource;
  - Tool to quantify severity of illness & Case Mix
  - Changes in ICU ‘epidemiology’
- Monitor outcomes when changing clinical/admin processes
- Compare and ICU’s performance over time
  - Adjusting to national ‘norms’
  - Adjusting to standard physiologic/organ function scores
- Benchmarking
  - Comparisons with other similar ICUs
  - National Datasets; UK, Scandinavia etc
- Research Purposes
  - Describes ICU population and sub-populations
  - Comparisons of ICU populations to others
  - Use in publications; required for modern research efforts.

Improve Outcome Predictions

Improving Performance; Neural Networks

Clermont, G, CCM, 2001
Additional Data to enhance Models

- Markers of inflammation
  - Serum amyloid A
  - Phospholipase A2
  - Neutrophil elastase
  - C-reactive protein
  - Interleukin 6 (failure to decrease from day 0 to 4)
  - Interleukin 6/10 ratios
  - TNF-alpha
  - Soluble TNF receptors
  - Antioxidant status
  - Microalbuminuria (albumin/creatinine ratio)
- Esophageal Doppler ultrasonography
- Tonometry

Sis-VistA; Automated severity scores

- 4651 cases, 442 deaths
- 6 ICUs in three Ohio VA hospitals
- Variables (APACHE): Age, comorbidity, Dx, Admit source (direct or transfer) & Lab results.
- aROC=.86, H-L stat; >.2
- Kappa=.78-.96 p<.001 computer abstracted and manually abstracted variables.
Process or Outcomes?

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Process versus Outcomes

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The School of Nursing
Vice Chair Critical Care

Disclosures

I have no relevant financial interest to disclose

The Answer is Both!

A Balanced Approach

Nearly half of physician care is not based on best practices:

Using recommended guidelines would help avoid harmful consequences:

- Hypertension: 68,000 avoidable deaths
- Heart Attack: 37,000 avoidable deaths
- Pneumonia: 10,000 avoidable deaths
- Colorectal cancer: 9,600 avoidable deaths

McGlynn et al, RAND 2003

Why not use the right tool?

Underlying Principles

- Must measure to improve
- Measurement for learning and testing, not for judgment
- Data do not improve processes, people do
Components of the system

Structure
- Presence of a smoking cessation program or materials

Process
- % of smoking patients given smoking cessation materials, total time spent in smoking cessation counseling

Outcome
- % of patients who quit smoking, cardiovascular event rates

Adapted from Donebedian

Examples

Structure
- Mandatory intensivist consultation/closed ICU
- Nursing to patient ratios maintained at 1:1 or 1:2

Process versus Outcome

Process
- More frequent updating
- Eligibility criteria required
- Shorter cycle time
- Small sample size
- Data collected during care
- Can often use clinical data
- Statistical help not needed

Outcome
- Less frequent updating
- Risk adjustment difficult
- Longer cycle time
- Larger sample size
- Follow up often required
- May need new datasets
- Requires statistical help

Additional Suggested Readings

Comparisons: Resources

• Process
  - More frequent updating
  - Eligibility criteria required
  - Shorter cycle time
  - Small sample size
  - Data collected during care
  - Can often use clinical data
  - Statistical help not needed

• Outcomes
  - Less frequent updating
  - Risk adjustment difficult
  - Longer cycle time
  - Larger sample size
  - Follow up often required
  - May need new datasets
  - Requires statistical help

Comparisons: Validity

• Process
  - Patients care less
  - Patients don’t understand
  - High face validity for providers

• Outcome
  - Patients care
  - Patients understand
  - Providers concerns that things outside their control impact these
Comparisons: Usability

• Process
  – Difficult inclusion and exclusion criteria
  – Hard to summarize measures
  – Feedback loop is clear

• Outcomes
  – Easy to define population
  – Often comparable across conditions
  – Hard to generate direct feedback for improvement
  – Benchmarking

Why are you in healthcare?

• I have never met a clinician who was interested in reducing LOS!
• We are interested in improving care and health
• Thus……..
  – Collecting data and managing the process is only important to us when either there is evidence of a connection to outcome or when its connection seems to be true at face value

4 Simple Upfront Questions

• Evidence to guide our practice
• Impact on morbidity and mortality
• Variation in practice
• Must be able to change practice

Pneumonia Processes Improved


Outcomes Improved


CRBSI Process & Outcomes

Keystone Project: >100 ICUs in Michigan
**Sepsis Bundle**

![Sepsis Bundle Chart]

VHA TICU 3 Project: 19 ICUs

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**Wake Up**

- **Process:**
  - Passing a daily screen of weaning parameters
- **Outcomes**
  - More likely to be successfully extubated (87% vs 30%)
  - More likely to survive (74% vs 29%)


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**Data Presentation: Dashboards**

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did we harm (BSI)</td>
<td>2.8/1000</td>
<td>0</td>
</tr>
<tr>
<td>How often do we do what we should</td>
<td>66%</td>
<td>95%</td>
</tr>
<tr>
<td>How often did we learn</td>
<td>100s</td>
<td>100s</td>
</tr>
<tr>
<td>% with strong Safety climate</td>
<td>16%</td>
<td>59%</td>
</tr>
<tr>
<td>Teamwork climate</td>
<td>18%</td>
<td>53%</td>
</tr>
</tbody>
</table>

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**Integrated Data Presentation**

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**Is there a common problem?**

- Is there a single thing or a small set of circumstances behind many of the errors/events that negatively impact patient care and outcome?

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**If there is it is……..**

COMMUNICATION
Communication breakdowns are frequently the root cause of undesirable outcomes.

Teamwork Climate Across Michigan ICUs

The strongest predictor of clinical excellence: caregivers feel comfortable speaking up if they perceive a problem with patient care.

RN Turnover and Teamwork Climate: 26 Keystone ICUs reporting

\[ r = -0.650, \alpha < 0.001 \]

Intensive Nursing Care Unit (INCU)
ITCU
Intensive Team Care Unit

Why not use the right tool?

A Balanced Scorecard

The Intensivist’s Role

Intensivist
Nursing PharmD
RT
NP/PA
Nutrition
PT/OT/Speech

Coxswain:
In charge of navigation, steering,
motivation, timing, rhythm, & .......
a servant
I Have Protocols, So Why Do I Need a Closed Unit?

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F. Mielck

“I have protocols, so why do I need a closed unit?” This seems to me a statement from somebody who don’t like critical care. But we like critical care!

The open unit concept. An open unit (as I understand it) is an ICU which is run by a permanent nursing team, competent in critical care. The nursing team is completed by specialists who are devoted to a whole spectrum of delimited tasks, such as respiratory therapy, clinical pharmacology, nutrition, infection etc. However, there are no specialised physicians directly assigned to the ICU. The medical treatment of the critically ill patients stays in the hands of the physician who is basically responsible for the treatment of the patient’s primary disease (but does this physician have knowledge and expertise in critical care?). So, finally, the critical care is done by the nurses. The head-nurse is responsible for the organisation of the ICU, but she/he has no influence on the medical decisions.

The specific critical care knowledge is fixed by protocols. Those protocols are necessary (a) to define the tasks and duties for all critical care providers (to compensate for missing expertise), (b) to ensure a treatment which is conform to the legal requirements (since legal prosecutions are much more pronounced in USA than in Europe).

Certainly, protocols are nowadays necessary, as they promote a treatment according to evidence based medicine. However, the disadvantage to completely rely on protocols is to my view that (a) in critical care the individual cases rarely are identical with the idealistic protocol situation, (b) often real cases have multilayered problems for which a mono-directed treatment by protocol is not adequate (e.g. sepsis, multiple organ failure), then (c) adaptation of the protocol to the individual problems again needs profound expertise (which often may not be available to general physicians).

One may argue, that the expertise, for instance in cardiac surgery, is best represented by the cardiac surgeon. This is certainly true in cases which stay on the main road of the basic disease. However, it may not be true if complications happen for which a special expertise in critical care is needed (e.g. septic shock).

The closed unit concept. A closed unit is an ICU where a competent team of physicians and nurses, experienced in critical care, is continuously available (24 hrs, 7 days a week) to treat the critically ill patients. They bring in their special expertise and combine this with the expertise of those who are responsible for the basic disease. Thus, the critical care expertise is always present, but the partners of the basic specialties still remain involved in the critical care treatment and can bring in their special input. Thus, it is a tight combination of expertise and responsibility.
The closed ICU is run as an organisational entity (in the following I will primarily describe the situation in our ICU in Germany): There is a director who is exclusively devoted to this commission, responsible for the entire critical care service (performance, personnel, budget, teaching & education, quality management, research, long-term development), to the patients and families, to the team, to the co-operating medical partners, to the hospital administration. He is specially trained and certified in critical care with many years of practical experience. He must possess special management capabilities, such as communication abilities, social competence, skills in staff leadership, process organisation, conflict management, and many others. So, he is a director on the same level as all the other clinical directors in the hospital with a special service mandate for critical care.

The team consists of nurses specially trained and experienced in critical care or trainees for this. They are permanently assigned for this job, or at least for some years. They perform their job in well organised three 8-hrs shifts, under the leadership of a nurse manager and a deputy manager per each shift. The physicians are either specialists in critical care (certified after a special training of two additional years, supplementing basic specialisation of e.g. anaesthesiology, surgery, internal medicine, pediatrics) or physicians in training for such specialisation. So, they stay in the ICU for longer terms. On the other hand there are younger physicians who spend a short ICU term (6 months) which is obligatory for any specialisation in the above mentioned four basic specialties. Anyway, there is a permanent team of physicians working full-time in the ICU, continuously 24 hrs per day in 8-hrs-shifts.

The potential advantages of the closed unit concept is:

- A competent team of nurses and physicians continuously on-site.
- Information (rounds, briefings, teaching) can be much better realized in a stable team (still difficult enough with so many staff members).
- Process organisation and optimization can be better achieved with a stable team.
- This facilitates quality management and improvement, equipment training, risk management, etc.
- This also facilitates continuous professional training and education, for nurses as well as for physicians.
- Last but not least - it makes possible a corporate identity which is the basis of an effective team-work and an optimal performance.

In general, I am sure that the closed unit concept provides more expertise for critical care, ensures a better treatment performance and cost-effectiveness, guarantees the adaptation of further medical and organisational development, and is the better way for medical education and training in critical care.

Protocols are good. They put in order the various treatment measures and ensure that the principles of evidence based medicine are maintained and nothing is missed. They are powerful and effective for all situations which can be standardized, such as the use of analgo-sedation [1], the weaning from ventilation etc. It has for instance been shown that protocol-driven weaning significantly shortens the time on mechanical ventilation compared to the treatment without weaning protocols [2]. Furthermore, to keep to protocols make sure that treatment is done according to the legal expectations. With this it is part of a strategy which we call “defensive medicine”. But, protocol driven critical care is not sufficient for more complicated situations.
**Why are good protocols not enough.** As protocols are designed for standard situations, all multilayered clinical problems will not be adequately solved. All situations in which several different problems must be weighed up need at least the additional knowledge and experience of an expert in critical care. The more multilayered an actual clinical situation is, the less important will often be the initiating problem or the underlying disease.

Think of the following example (*I will demonstrate the European view in my comments*):

A 55-yrs old male became septic as a complication after abdominal surgery (*Of course this the surgeon’s special task: he carried out repeated surgical interventions*). Fluid replacement and vasopressor therapy was given from the beginning on (*is that the surgeon’s job? NO! This is critical care treatment, done by those who are continuously at bed-side*). But, despite the surgical interventions septic shock developed. Renal function failed, renal replacement therapy (CRRT) had to be initiated (*Do we now need a nephrologist who may not be familiar with the patient’s problems? NO! Again this will be decided and carried out by the ICU team who is used to handle CRRT*).

Off course, we can wait for the decision for CRRT until the nephrologist has arrived; however, we will lose much time. And will he be present at the ICU all time when the patient is on CRRT? NO! So, we are happy for his special expertise and we will call him, if we need his advice. But we will perform the CRRT with all its various small problems which occur during treatment and which we are familiar with.

For such situations (significant for more pronounced critical care problems) there are sometimes guidelines available which present the relevant evidence based study results. An excellent example for this are the practice guidelines of the Surviving Sepsis Campaign [3]. But guidelines are not protocols, they only present the actual knowledge, they are not direct instructions for treatment, they need to be interpreted by the critical care specialists.

**Good critical care means fast reaction, availability around the clock.** There is now clear evidence that a fast reaction is the key point of optimal critical care. A good example for this is the early-goal directed therapy for severe sepsis [4]: when cardiac function and oxygen delivery could be optimized within the first 6 hours by adequate fluid and catecholamine therapy, hospital mortality was improved (30.5% compared to 46.5% after standard therapy, risk adjusted). Even more instructive is an analysis of the pre-treatment period from two large sepsis studies [5]. The risk-adjusted analysis shows that if fast adequate treatment of severe sepsis results in an improvement within the first 24 hrs, there will be a considerable reduction of the 28-days mortality. The basic insight from this study might seem banal, but it is so important: “If it doesn’t get better, it is worse!” And we should not forget that every complication *per se* prolong the length of stay in the ICU and costs money!

Fast, adequate reaction can only be established by a **devoted ICU staff** of nurses and physicians, continuously present in the ICU (service 24 hrs a day, 7 days a week). The ICU team on-site must be capable and legitimated to make the decisions immediately required. It must be able to act without lengthy and delayed decision processes. Often, it is impossible and/or risky to postpone the necessary reactions until an external expert has been asked; he may even be actually unavailable because being busy in the OR. So, there are simple reasons why the closed unit with a competent, experienced ICU staff (physicians and nurses) is more effective.
Closed units are more effective. Well-known is the meta-analysis of Pronovost and coworkers [6]: They were able to show that “high-intensity staffing” (critical care team with an intensivist / obligatory consultation) revealed lower ICU and hospital mortality, and shorter hospital length-of-stay.

The closed unit concept is the usual concept of critical care in Europe.

Who “owns” critical care in Europe?
In some countries, such as Scandinavia, Italy, and some East-European countries critical care is a subspecialty of anaesthesiology, exclusively. However, in most European countries it is open also for other specialties, such as internal medicine, surgery, neurology, pediatrics and others [7]. This is a concept which can be called “supra-specialty” (critical care situated above the basic specialties). Only in two European countries there is a special situation: In Spain critical care is a specialty by its own, and in Switzerland basic specialists can achieve an additional independent specialisation in critical care.

To my view, the “ownership” of critical care is closely linked to the monetary interest: In Germany (where I know the situation the best) the reimbursement (DRG based) of critical care treatment is income of the hospital. The physicians are paid by standard wages. The ICU director is also paid by the hospital (salary); additionally he gets a moderate extra pay for private patients in the ICU. Formerly, this extra pay was a considerable part of his income. However, this has changed during the last ten years. So, from the monetary interest the ICU is not really attractive anymore. What makes so many directors (surgeons, anaesthesiologists, internists, neurologists, etc.) keen on possessing an ICU, is more the question of professional power, of “glamour”, of being independent from others (e.g. availability of ICU beds), etc.

Nevertheless, in large German teaching hospitals there is now a progressive trend to concentrate the different isolated, specialty-related ICUs into one multidisciplinary centre for critical care. A trend which is driven forward by the hospital administrations with the aim to achieve better cost-effectiveness and quality.

The multidisciplinary Centre for Critical Care. Six years ago I had to organize such a new centre for surgical critical care, four previously isolated ICUs (one for neurosurgery, one for cardiac surgery, two for anaesthesiology) merged into one central unit. The centre with now 42 beds under the leadership of one director is staffed by 30 physicians [10 attendees (2 senior, 8 junior), 20 residents (12 from anaesthesiology, 4 from cardio-thoracic surgery, 2 from neurosurgery, 2 from trauma surgery)]. Nursing staff consists of 170 nurses (~1 nurse per bed per shift, + 25% for vacation and sick-leave), 2 nurse managers, 4 deputy nurse managers. The centre takes care of surgical critical care patients from trauma surgery, neurosurgery, cardio-thoracic surgery, abdominal surgery, transplantations, ENT, urology, gynecology, orthopedics, and some non-surgical patients. In 2006, 4059 critically ill patients were treated with a mean LOS of 3.6 d (ICU mortality = 5.8%). The ICU beds were occupied to 94.5%.

This concept is now going to be realized also in several other university hospitals and large teaching hospitals. However, this is subject to some reservation and concern within the various specialties which are afraid to loose their own influence on critical care. Indeed, such multidisciplinary ICUs are often run and headed by anaesthesiologists who are much more frequently specialised also for critical care than other specialists (36% of anaesthesiologists have additional certification for critical care).
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References


Interactive Clinical Forum
Avery Tung, M.D. Moderator

Discussants:
M.F. O’Connor, M.D.
A. Shander, M.D.
M. Avidan, MBCh, DA, FCA
A. Friedrich, M.D.

A 59 y/o female with metastatic ovarian cancer undergoes pelvic exenteration under GA.

Her past medical history includes COPD, CHF, OSA, HTN on an ACEI, obesity, and NIDDM. She has previously undergone radiation and chemotherapy (Mitoxantrone). She has no allergies, and was taking Enalapril, Lasix, Metoprolol, Metformin, inhaled Beclomethasone and Albuterol 2x/day preoperatively.

She has previously had GA for a knee arthroscopy and sedation for a colonscopy. Her exercise tolerance was fair...she had to rest after climbing 1 flight of stairs...but can walk 3 blocks and work in the garden without difficulty breathing. She can lay flat. An echocardiogram done 6 months ago reveals EF=35%, mild MR

Her preoperative vital signs were: HR 79, BP 150/90, RR 20. SpO2 on RA was 93%. BMI = 30 (86kg, 5’5”) with mild ascites on CT scan. Hct 41%, Cr 1.2, HCO3 = 34 meq/dl, K = 3.5.

The case was 8 hours long. EBL was 500cc, 800cc ascites were drained, and U/O was 170cc. Total intake included 6.5L crystalloid, 3U PRBC, 2FFP.

Abg 1 hr prior to case end was 7.32/41/128 on 100% FiO2

The patient was left intubated and brought to the ICU postoperatively. On admission, she was sedated and unresponsive. BP 108/40, HR 105. Her lines include 2 18G IVs and a R radial arterial line. Abg: 7.30/45/82 on 50% with PIP = 42 cm H2O. BE = -5, Hct = 28, HCO3 = 19.

a. **Perioperative beta blockade in patients chronically on beta blockade is now a SCIP measure. This patient was on a beta blocker preoperatively. Would you restart beta blockers at this time?**


2. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM.
Perioperative beta-blocker therapy and mortality after major noncardiac surgery.

Am Heart J. 2006 Nov;152(5):983-90


b. Would you implement lung protective ventilation in this patient (PIP <30)?


Am J Respir Crit Care Med. 2002 Dec 1;166(11):1510-4.

3. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O. What tidal volumes should be used in patients without acute lung injury?
Anesthesiology. 2007 Jun;106(6):1226-31


Am J Respir Crit Care Med. 2003 May 15;167(10):1304-9

c. This patient has no central access. Would you place a central line?

Over next 4 hours U/O (cc per hour) is low: 15, 15, 10, 5 despite Lactated Ringers infusing at 150cc/hr IV. BP 105/60, HR 95, JPs draining 100/hr serosanguinous fluid, Abg 7.28/45/85 on 60%.

The urine output is low. How would you react:

a. Continue to observe
b. Crystalloid 500cc IV fluid bolus
c. Albumin 250cc IV fluid bolus
d. More information?


You elect to seek more hemodynamic information:

b. Which hemodynamic monitor would you choose?
   a. Echocardiogram
   b. CVP
   c. PA catheter

c. Which measure of circulatory function would you want?
   a. SvO2 >65%
   b. CVP >13
   c. Lactate < 2.0
   d. U/O >20 cc/hr


CXR now shows mild pulmonary edema. Abg now 7.26/52/60 on 60%. PIP = 36 and Hct = 26%. CVP = 14

a. Would you transfuse this patient?


The patient develops sepsis and ARDS. After 6 days, bowel function has not yet returned. Prealbumin = 11 and AM glucose = 196

a. Would you begin TPN?

b. Would you initiate an insulin drip?


Resistant Infections in the ICU: What Can/Should the Intensivist Do?

Antibiotic Resistance

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Before modern times humans had little understanding about infection and were subject to multiple devastating pandemics, such as the Black Death of the fourteenth century. The following timeline presents some of the milestones that have advanced our ability to combat infection over the past millennia:

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>1675</td>
<td>Antony van Leeuwenhoek discovered bacteria.</td>
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<tr>
<td>1796</td>
<td>Edward Jenner laid the foundation for vaccines.</td>
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<tr>
<td>1848</td>
<td>Ignaz Semmelweis discovered hand washing could prevent infection or contagion.</td>
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<tr>
<td>1857</td>
<td>Louis Pasteur introduced the germ theory of disease.</td>
</tr>
<tr>
<td>1867</td>
<td>Joseph Lister pioneered antiseptics during surgery.</td>
</tr>
<tr>
<td>1876</td>
<td>Robert Koch, by studying anthrax, showed the role of bacteria in disease. Dmitri Ivanovski discovered viruses.</td>
</tr>
<tr>
<td>1892</td>
<td>Alexander Fleming discovered penicillin.</td>
</tr>
<tr>
<td>1928</td>
<td>Jonas Salk developed polio vaccine.</td>
</tr>
<tr>
<td>1955</td>
<td>Luc Montagnier and Robert Gallo identified the virus that causes AIDS.</td>
</tr>
<tr>
<td>1983</td>
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The increase in resistance of human pathogens to antimicrobial agents is one of the best-documented examples of evolution in action at the present time. Since the discovery of penicillin in 1928 bacteria have undergone more mutations than have humans since we split millions of years ago from our ancestor in-common with apes. In the past 40 years, there have been only two new antibiotic chemical classes: oxazolidinones (linezolid) and lipopeptides (daptomycin). Most classes of antibiotic were discovered in the 1940s and 1950s, and are directed at a few specific aspects of bacterial physiology — biosynthesis of the cell wall, and of DNA and proteins. Pharmaceutical companies have generally retreated from antibacterial drugs, concentrating on chronic diseases in the interests of maximum profits. One of the reasons for widespread drug resistance among bacterial pathogens is owing to the limited choice of antibiotics that exploit a relatively narrow range of mechanisms. It is encouraging that there are some new developments in the offing, such as the discovery of a small molecule, platensimycin, derived from Streptomyces platensis that targets a seldom-exploited weakness in bacteria: fatty-acid biosynthesis. Such discoveries offer some consolation in the battle with resistant and emerging infections. Hopefully this discovery will be translated into the development of new anti-microbial agents.

In recent decades many new infections have either been discovered or have “emerged.” Examples of emerging infectious diseases are shown below:
**Bacteria**
*Bartonella henselae*: cat-scratch disease
*Borrelia burgdorferi*: Lyme disease
*Ehrlichia chaffeensis*: Ehrlichiosis (a form of “tick-bite fever”)
*Helicobacter pylori*: peptic ulcer disease

**Viruses**
Ebola viruses: hemorrhagic fever
Hantaviruses: hemorrhagic fever
Hepatitis C virus: chronic hepatitis, cirrhosis
Hepatitis E virus: acute hepatitis
Human herpesvirus 6: roseola, infection in the immunocompromised
Human herpesvirus 8: Kaposi’s sarcoma
Human immunodeficiency virus: Acquired Immunodeficiency Syndrome (AIDS)
Nipah virus: encephalitis
Parvovirus B19: Fifth disease, arthritis, anemia
SARS coronavirus: severe acute respiratory syndrome
H5N1 Influenza A: severe influenza

**Parasites**
Babesia protozoa: Babesiosis (“Redwater Fever”, a form of “tick-bite fever”)

What is perhaps even more concerning is that infectious diseases that appeared to be vanquished, such as tuberculosis (TB) and malaria, are having an alarming resurgence. Some reemerging pathogens, such as multi-drug resistant tuberculosis (MDR-TB) and Extensively Drug Resistant tuberculosis (XDR-TB), have evolved resistance to previously successful antimicrobial therapy. Such trends are a cause for concern for the World Health Organization.

Multi-drug resistant organisms cause an increasing number of bacterial infections in hospitals. Bacteria are emerging with resistance to all available antibiotics. Examples include *Pseudomonas aeruginosa, Burkholderia cepacia, Acinetobacter baumanii, Stenotrophomonas maltophilia, Enterobacter cloacae, Serratia marcescens* and *Klebsiella pneumoniae*.²

Much of the attention is presently focused on resistant Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus*. But even if vancomycin fails, there are new drugs for Gram-positive organisms such as linezolid and perhaps platensimycin in future. Disturbingly, there is a near-total lack of developmental antibiotics active against the resistant Gram-negative pathogens referred to above.⁴

**Resistance Mechanisms** (Figure 1)
Resistance to antibiotics occurs through several mechanisms: i) Inactivation (e.g. specific enzymes); ii) Modification of drug targets; iii) metabolic modification; iv) reducing the influx of antibiotics; and v) efflux pumps.⁵ The resistome is the pool genes coding for resistance and may suggest that rapid emergence of resistance to antibiotics is inevitable.⁵ Resistance genes already exist to any class of antibiotic, including novel antibiotics! The resistome (see Glossary) is comprehensive, adaptable and
extensive. The implications for the emergence of resistance in pathogenic bacteria are significant given the potential ability of genes to be mobilized through the pan-microbial genome.\textsuperscript{5} Bacteria exchange genetic information through: i) direct uptake of DNA (transformation); ii) phage-mediated transduction; iii) inter-organism contact with DNA exchange (conjugation) iv) mobilization of DNA within organisms' genomes (transposition).

**MRSA**

*Staphylococcus aureus* is part of the normal flora of the skin and anterior nares. It is a common cause of infection in humans, particularly of skin and soft tissue, bone and joint. Methicillin resistance develops in *S. aureus* due to the acquisition of a large mobile genetic element, which carries the *mecA* gene. This gene encodes for PBP2’, which permits cell wall synthesis in the presence of beta-lactam antibiotics, including flucloxacillin and nafcillin. (Figure 1) Strains of *S. aureus* with methicillin resistance are not necessarily more virulent than strains that are susceptible, but MRSA strains are more prevalent in hospitals because of epidemic spread and selection through the use of broad-spectrum antibiotics.

Acquisition of MRSA by a patient in hospital results in replacement of their normal staphylococcal flora with MRSA. MRSA colonization can then be detected on skin (especially in moist places, such as armpits and groins), in the throat, on devices (such as intravenous or urinary catheters) and on any wounds or ulcers. MRSA is generally treated with the glycopeptide antibiotics, vancomycin and teicoplanin. These antibiotics can only be given intravenously. Following identification of MRSA bacteremia, a course of 2–4 weeks of intravenous treatment is necessary as it is usually presumed that an endovascular source of infection has been established by *S. aureus*. Oral courses of therapy are not usually given for MRSA, but agents such as rifampicin, doxycycline, sulphamethoxazole–trimethoprim and fusidin may have a role depending on the susceptibility pattern of the strain.

**VRE**

Enterococci are part of the normal bowel flora. They are increasingly responsible for colonization and infection in hospitals, as they are resistant to many groups of antibiotics. Enterococci usually show moderate innate resistance to penicillins, cephalosporins, clindamycin, aminoglycosides, sulphamethoxazole and fluoroquinolones. *Enterococcus faecalis* is normally susceptible to ampicillin, and *E. faecium* to vancomycin, but there has been epidemic spread, especially in US hospitals, of a strain of *E. faecium* with high-level resistance to vancomycin.

Vancomycin resistance is due to the possession of the *vanA* gene, which mediates the replacement of D-alanyl-Dalanine linkages of the growing cell wall with D-alanyl-D-lactate. Glycopeptide antibiotics cannot bind to D-ala-D-lactate, and organisms producing *vanA* are therefore resistant. (Figure 1) Enterococci, including VRE, have low virulence, so tend to cause infections in hosts with compromised defences. Epidemics of infection occur in hematology, renal and intensive care units. High antibiotic use, especially with cephalosporins and vancomycin, is thought to be an important predisposing factor. Most affected cases have colonization only, but about 10% will suffer a serious invasive infection, for which few therapeutic options are available. Some strains of VRE are susceptible to teicoplanin. Otherwise, treatment with chloramphenicol may be effective, and linezolid and quinupristin–dalfopristin are generally active. Occasional cases have been treated with very high doses of ampicillin (> 300 mg/kg/day). Simple measures can save lives. A study compared the use of
‘gloves and gowns’ with ‘gloves only’ donned when entering the rooms of patients colonized with VRE. It was estimated that 58 cases of VRE colonization and six cases of VRE bacteremia were averted by the use of ‘gloves and gowns’.6

Figure 1: Mechanisms of Antibiotic Resistance

**New drugs for MRSA and VRE**
In recent years, three agents with activity against resistant Gram-positive bacteria have been developed, Synercid® (dalfopristin–quinupristin, a streptogramin), linezolid (oxazolidinone) and daptomycin (cyclic lipopeptide). These agents are also active against many strains of VRE. Linezolid can be administered orally as well as intravenously, which represents a breakthrough in management. These agents are generally reserved for special cases, especially MRSA and VRE, following the recommendation of an infectious disease physician or clinical microbiologist, and sometimes represent the final therapeutic opportunity for some difficult to treat infections.

**Hope for the Future**
Hope in the post antibiotic era lies in the development of new antibiotics and in alternative strategies to antibiotics. Alternatives to antibiotics that are being explored include immunotherapy, non-pathogen-specific immunomodulatory therapy, phage therapy, bacteriocin therapy, inhibitors of virulence factors, preventing LexA cleavage (inhibition of mutation)', exploiting plants and the ocean, anti-adhesin
Bacteriophages are a specific type of virus that only targets bacteria. Research suggests several types of bacteriophage for each type of bacterium have evolved. Antibiotics kill non-specifically and have side effects. Species specificity is the rule for phages. A polyvalent phage is a virus that infects many strains within a bacterial species. Important human bacterial pathogens owe their virulence to prophages that are integrated into their genomes. Phage therapy should therefore come from obligate lytic phages that do not have integrases and cannot “integrate” into the bacteria. Phages become diluted in absence of a target bacterium and self-amplify in the presence of target pathogen. Anti-adhesin strategies may prevent bacteria from binding to host surface receptors thereby rendering the bacteria harmless. Riboswitches in bacterial mRNAs form receptors that bind specific metabolites to control the expression of genes involved in metabolite biosynthesis and transport. Blocking riboswitch binding could halt the expression of essential genes.

Current antibiotics act against one of only four cellular processes, & bacteria have found ways to compensate for them all. New drugs with novel mechanisms of action are therefore urgently needed. But identifying drug targets that are essential for bacterial survival, are conserved across species and lack a human homologue is a significant challenge.

**Antibiotic Resistance:**

- New infections are emerging at an alarming rate.
- Old infections, such as TB, are reemerging with resistance to treatment.
- Increasing numbers of Gram-negative bacteria are resistant to all antibiotics.
- Resistance becomes more dangerous when virulent organisms acquire antimicrobial resistance.
- Resistance among virulent Gram-positive organisms, such as *Streptococcus pneumoniae* and *Staphylococcus aureus* is increasing.
- No new drugs are being developed to target resistant Gram-negative organisms.
- New antibiotic and non antibiotic strategies are urgently needed to combat resistant organisms.

**Glossary:**

*Superbug* - Pathogen resistant to multiple antibiotics.

*Resistome* - All the resistance genes and their precursors in pathogenic and non-pathogenic bacteria.

*Cryptic resistance gene* - Embedded in bacterial chromosome, but not obviously associated with resistance. Not expressed, or expressed at low levels.

*R-plasmid* - In bacterial pathogens and environmental microorganisms, and contains antibiotic resistance genes.

**Key Web sites:**

http://www.nature.com/focus/antibacterials

http://www.tufts.edu/med/apua/

http://www.cdc.gov/drugresistance/

http://www.who.int/mediacentre/factsheets/fs194/en/

http://www.who.int/topics/drug_resistance/en/
References:
Sepsis: What’s New in Basic Science Update

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There are a broad range of investigations underway to understand the basic mechanisms of sepsis and to define new therapeutic targets. A large proportion of prior sepsis studies focused on early inflammatory aspects of sepsis, but anti-inflammatory mediator therapies for the most part did not show resounding efficacy in large clinical trials. Current basic studies are focused on the roles of molecular, cellular, metabolic, and physiological factors in sepsis. Data derived from basic studies in each of these areas have led to promising potential therapeutic targets.

Toll-like receptors (TLRs) are a family of receptors that recognize conserved molecular motifs in microorganisms, and are critical in sensing and generating early inflammatory responses to infection (1, 2). At least 10 TLRs have been identified in humans. TLR4 mediates the inflammatory effects of endotoxin (LPS) from Gram-negative bacteria, and TLR2, mediates the inflammatory effects of lipoproteins from Gram-negative bacteria, and also of components of Gram-positive bacteria and fungi (3, 4). Studies suggest that TLR-mediated pathways are important in sepsis-induced cardiovascular and pulmonary dysfunction (5, 6). TLR2 and TLR4 are being intensively investigated in the context of sepsis and sepsis-induced organ dysfunction, and as potential targets for anti-sepsis therapies.

Investigators are also focusing on the intracellular pathways involved in TLR-mediated activation of inflammation. NF-κB, has been extensively investigated, and is an important intracellular mediator of TLR-induced inflammation (7, 8). NF-κB is a nuclear transcription factor that regulates inflammatory gene expression. Animal studies have yielded promising results with respect to interfering with NF-κB transcriptional activities. Another transcriptional regulatory protein, activating protein-1 (AP-1) is also being investigated as a potential mediator of sepsis and as a target for anti-sepsis therapies (8, 9). Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcription factor that is involved in regulating redox balance and stress response. Studies suggest the Nrf2 is involved in protection against sepsis-induced inflammation and death, raising the possibility that this transcription factor could be a future novel target for antisepsis therapies (10).

Metabolic factors are believed to be extremely important in sepsis. Mitochondrial dysfunction has been implicated in the pathogenesis of sepsis-induced organ dysfunction (11). Studies suggest that cytochrome C may be important in mitochondrial dysfunction, and investigators are exploring cytochrome C as a potential therapeutic target (12). The normal balance between the formation and removal of reactive oxygen species (ROS) is disrupted in sepsis resulting in oxidative stress. ROS scavengers have been shown to attenuate effects of endotoxin in animal studies (13). Antioxidants, such as N-acetylcysteine, lazaroids, and pyrrolidine dithiocarbamate are being explored as potential therapies against the oxidative stress that likely contributes to sepsis-induced organ failure (14).
Statins have a variety of different effects that may contribute to improved outcome in sepsis, including anti-inflammatory, immunomodulatory, and anticoagulant effects (15). A number of clinical studies suggest that statins may provide survival advantage in human sepsis. Animal studies also support the further exploration of statins in sepsis (16).

There have been tremendous advances over the last several decades in understanding the basic science of sepsis. However, the overall mortality due to sepsis has not changed substantially, which underscores the need to continue with intensive basic investigations into the pathophysiology of sepsis and sepsis-induced organ dysfunction.

References


Pro-Con – Simulation: Should It Be Part of ICU Training?

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