Protocols: The Good, the Bad and the Ugly

Nicholas Sadovnikoff, M.D.
Brigham and Women's Hospital
Boston, Massachusetts

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[i] 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[ii] 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[iii] and 2000[iv], 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[v] 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[vi] 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 Berghe 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[vii] 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 punition). 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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[i] Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med 1991; 324:1445-1450.
[ii] Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996; 335:1864-1869
[iii] Ely EW, Bennett PA, Bowton DL, et al. Large scale implementation of a respiratory therapist-driven protocol for ventilator weaning. Am J Respir Crit Care Med 1999; 159: 439-446.
[iv] Marelich GP, Murin S, Battistella F, et al. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: Effect in weaning time and incidence of ventilator-associated pneumonia. Cheat 2000; 118:459-467.
[v] Krishnan J, Moore D, Robeson C, et al. A prospective, controlled trial of a protocol-based strategy to discontinue mechanical ventilation. Am J Respir Crit Care Med 2004; 169: 673-678.
[vi] Tanios MA, Nevins ML, Hendra KP, et al. A randomized controlled trial of the role of weaning predictors in clinical decision making. Crit Care Med 2006; 34:2350-2535.
[vii] Timmermans S. From autonomy to accountability: The role of clinical practice guidelines in professional power. Perspectives in Biology and Medicine. 2005; 48:490-501.

Prognosis Scores: Better Care?

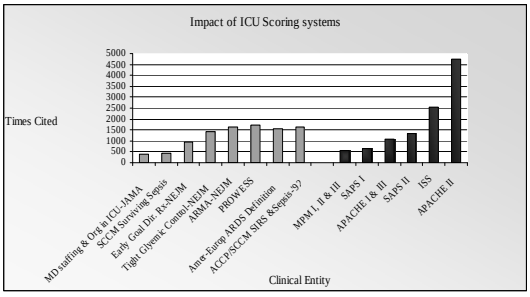
Andrew L. Rosenberg, M.D.
University of Michigan
Ann Arbor, Michigan

ICU Scoring Systems: Better Care?

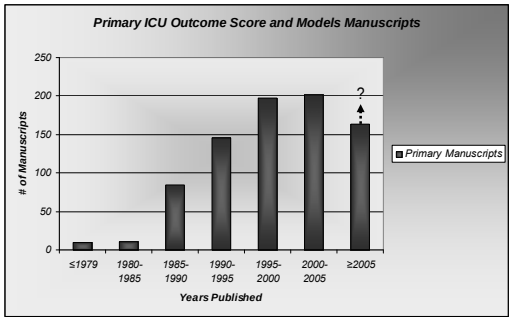
Andrew Rosenberg MD

Chief, Division of Critical Care
Department of Anesthesiology
University of Michigan

Comparison of Citations for Leading Clinical and Scoring System Manuscripts



Manuscripts Focusing on ICU Scoring Systems, Prognostic & Outcome Models



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

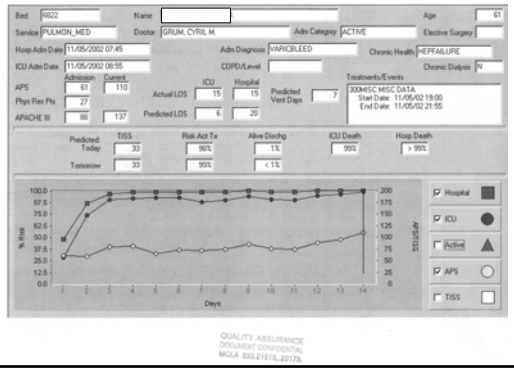
- ***General ICU Outcome Models***
  - *Case-mix, physiologic Derangement*
    - *APACHE; Acute Physiology, Age, Chronic Health Evaluation*
      - *APACHE, APACHE-II, APACHE-III (I & J), APACHE-IV*
    - *SAPS; Simplified Acute Physiology Score*
      - *SAPS I, SAPS II, SAPS-III*
    - *MPM; Mortality Probability Model*
      - *Admit, 24 hr, 48hr, 72 hr, over-time,*
    - *TRIOS (Three days Recalibrated ICU Outcome Score)*
    - *PRISM; Pediatric RISK of Mortality*
    - *PIM I&II; Pediatric Index of Mortality*
    - *DORA; Dynamic Objective Risk Assessment*
- *Organ system failure*
  - *MODS; Multiple Organ Dysfunction Score*
  - *LODS; Logistic Organ Dysfunction system;*
  - *SOFA; Sequential Organ Failure Assessment*
  - *Brussels*
  - *ODIN= Organ Dysfunctions and/or Infection*
  - *P-MODS; Pediatric Multiple organ Dysfunction Score*
  - *PELOD; Pediatric Logistic organ dysfunction*
- *Chronic Health*
  - *Charleston Index*
- *Therapeutic Intervention nursing ICU scores;*
  - *TISS; Therapeutic Intervention Scoring System*
    - *TISS-28; simplified*
    - *NTISS; neonatal therapeutic intervention scoring.*

SFAR; 2007

Surgical & Disease Specific ICU Scores

- *General surgical*
  - *APACHE, MPM*
  - *POSSUM; Physiologic 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*
  - *Parsonnet*
  - *EUROSCORE*
  - *System 97 score; cardiac surgery*
  - *OMMI; coronary surgery*
  - *IRISS;graft failure after lung Tx.*
  - *Lung Resection Score; thoracic surgery*
- *Disease Specific*
  - *Neuro*
    - *GCS*
    - *SAH scores; Hunt-Hess*
    - *RASS, RAMsay, CAM-ICU*
  - *Cardiac*
    - *AHA cardiac risk-Lee Goldman*
  - *Respiratory/Pulmonary*
    - *Murray Score*
  - *Renal*
    - *Dye Induced Renal Failure*
    - *RIFLE Score; ARF*
  - *GI/Hepatic*
    - *Ransons*
    - *Child-Turcotte*
    - *MELD*
  - *Sepsis*
    - *PIRO*

Individual ICU Pt. Screen



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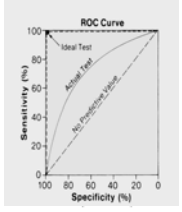
Comparison of Severity Models on a common data set

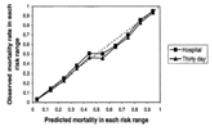
Model	aROC	Calibration GOF (HStatistic)	Sample Size
APACHE II	.853	.0001	12899
APACHE III	.848	NA	12899
MPM0-1	.766	.0001	4605
MPM0-II	.805	.014	4605
MPM24-I	.815	.0001	4101
MPM24-II	.833	.0247	4101
SAPS-I	.784	NA	4605
SAPS-II	.847	.1019	4605

Castella, X, CCM 1995

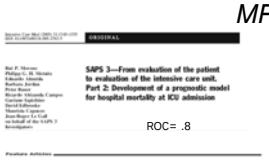
Statistics for ICU Scoring Systems

- ***Logistic Regression***
  - $y_{(logit)} = ß_0 + ß_{1X1} + ß_{2X2} + \ldots\ldots ß_{pXp} + \varepsilon$
  - $prob. = e^y/1 + e^y$
- ***Discrimination****= how the model distinguishes pts who die from those who live based on estimated probabilities of mortality*
  - *0.5 to 1*
  - *Receiver Operator Curves*
- ***Calibration****= observed to predicted outcomes across deciles of mortality risk*
  - *Hosmer-Lemeshow test (C-statistic) want the P value to be >.05*





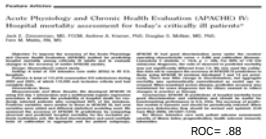
Updated Models: APACHE IV, SAPs III, MPM



SAPS 3—From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission

ROC= .8

- *16,784 patients*
- *303 ICUS*
- *10-2002 to 12-2002*
- *1. 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.*



Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients*

ROC= .88

- *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*
  - *PaO2:FiO2 ratio*
  - *Receiving mechanical ventilation*
  - *MI rec'ing thrombolytics*

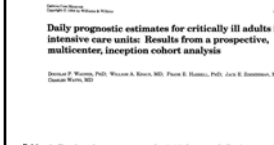
Assessing contemporary intensive care unit outcome: An updated Mortality Probability Admission Model (MPM_0-III)*

Thomas L. Higgins, MD, MBA, FCCM; Daniel Teres, MD, FCCM; Wayne S. Copes, PhD; Brian H. Nathanson, PhD; Maureen Stark, MSc; Andrew A. Kramer, PhD

ROC= .823

Project IMPACT database
124,885 patients
135 ICU's
98 Hospitals 10-2001 to 3-2004
H-L= 11.62, p=.03

Daily Scores



Daily prognostic estimates for critically ill adults in intensive care units: Results from a prospective, multicenter, inception cohort analysis

Table 3. Total explanatory power for initial seven daily Acute Physiology and Chronic Health Evaluation (APACHE) III intensive care unit (ICU) predictive equations. Receiver operating characteristics (ROC) and R^2 are two different measures of the amount of variation accounted for by each day's equation. The larger the ROC area and R^2 value, the greater the explanatory power

ICU Day	ROC Area	R^2
1	.90	.40
2	.89	.39
3	.88	.39
4	.87	.39
5	.86	.37
6	.84	.34
7	.84	.35

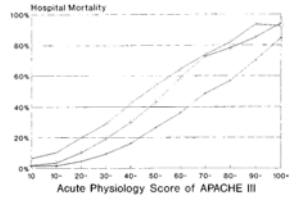


Figure 3. Relationship between Acute Physiology Score on a given day and observed hospital mortality rate for patients remaining in the intensive care unit during day 1 (n = 17,440, *dots*); day 2 (n = 14,034, *plus signs*); and day 6 (n = 3,137, *diamonds*). *APACHE*, Acute Physiology and Chronic Health Evaluation.

Organ Failure Scores; SOFA

Variables	0	1	2	3	4
Resp; Pa02/Fi02	>400	<400	<300	<200	<100
Coag; Platelets	>150	<150	<100	<50	<20
Liver;Bilirubin	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
CV; Hypotension	None	MAP <70	Dop<5 mcg/kg/min or Dobutamine	Dop>5 mcg/kg/min, epi<.01 or Norepi<.01	Dop>15 mcg/kg/min, epi >.01, norepi>.01
CNS; GCS	15	13-14	10-12	6-9	<6
Renal; Creat or UO	<1.2	1.2-1.9	2.0-3.4	3.5-4.9, <500	>5.0 or <200

Ferreira, FL, et al. JAMA 01

Organ Failure Scores; SOFA

ORIGINAL

Multicenter study of the multiple organ dysfunction syndrome in intensive care units: the usefulness of Sequential Organ Failure Assessment scores in decision making

79 ICU

1340/7615 patients with MODS

In hosp mort for MODS=45%

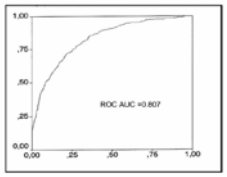
100% mortality in patients with;

Age>60

SOFA >13 on d1-5

Minimum SOFA >10

Positive or unchanged SOFA from day 1-5



Maximum SOFA

ORIGINAL

The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study

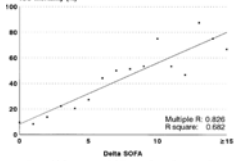
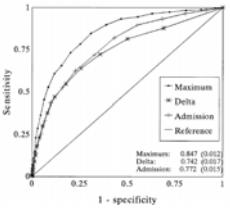


Fig. 5 Delta SOFA score and ICU mortality. A linear relation exists between delta SOFA and ICU mortality

Fig. 4 Discriminative power of total maximum SOFA score, delta SOFA and admission total SOFA score. The receiver operating characteristics (ROC) curve summarises the relationship between sensitivity (number of true positives) and 1 minus specificity (number of false positives) for all the possible values of the score. The reference line represents the discriminative power of a score no better than chance (area under ROC curve 0.5). The values within brackets are standard errors. The outcome used was vital status at ICU discharge

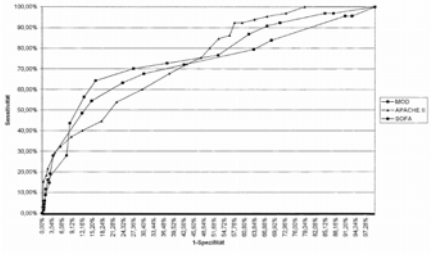


Scores and Clinical Care: Physiologic vs Organ Failure

874 SICU patients

1 German hospital

ROC= AII=.73, MOD=.77, SOFA=.71

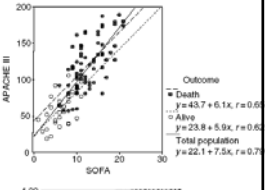


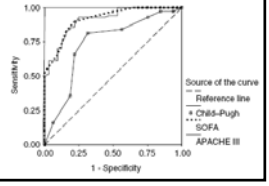
Hanke, Chirug, 2000

Organ failure vs Physiologic Scores

ORIGINAL PAPER

Prospective cohort study comparing sequential organ failure assessment and acute physiology, age, chronic health evaluation III scoring systems for hospital mortality prediction in critically ill cirrhotic patients





Clinician vs. Computer Predictions

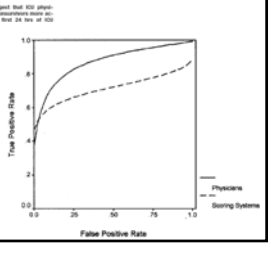
Mortality predictions in the intensive care unit: Comparing physicians with scoring systems*

Tasnim Sinuff, MD; Neill K. J. Adhikari, MD; Deborah J. Cook, MD; Holger J. Schünemann, PhD; Lauren E. Griffith, MSc; Graeme Rocker, MD; Stephen D. Walter, PhD

12 Studies

aROC for physicians = .85

aROC for Scoring Systems,= .63 p=.002



Influence of Clinician's prediction and the final outcome

Clinician predictions of intensive care unit mortality*

Graeme Rocker, DM; Deborah Cook, MD; Peter Sjokvist, MD†; Bruce Weaver, MSc; Simon Finfer, MD; Ellen McDonald, RN; John Marshall, MD; Anne Kirby, MD; Mitchell Levy, MD; Peter Dodek, MD; Daren Heyland, MD; Gordon Guyatt, MD; for the Level of Care Study Investigators and the Canadian Critical Care Trials Group

Table 2. Factors predicting intensive care unit (ICU) mortality for 851mechanically ventilated patients

Independent Predictors of Mortality	HR (95% CI)	*p* Value
Admission illness severity		
APACHE II score (5-unit increments)	1.16 (1.08–1.24)	<.001
Daily factors		
MODS (5-unit increments)	2.50 (2.06–3.04)	<.001
Inotropic agents or vasopressors	2.14 (1.66–2.77)	<.001
Dialysis	0.51 (0.35–0.75)	.001
Patient preference to limit life support	10.22 (7.38–14.16)	<.001
Clinician prediction		
Physician prediction of ICU survival <10%	16.77 (8.54–32.92)	<.001

CCM, 2004

Scores and End of Life Care; PIC

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

Bekele Afessa, MD, FCCP; Mark T. Keegan, MB, MRCPI; Zulfiqar Mohammad, MD; Javier D. Finkielman, MD; and Steve G. Peters, MD, FCCP

302 adults with day 1 Predicted mortality >80%

Day 1 pred. Hosp Mort= 88%, Day 3 pred. Hosp. Mort=87%

Actual= 61%

Day 3 aps> day 1 aps in 34/302= 11%

32/34 patients died, and only 1 survied >100days.

Sens= 15%, Specificity= 99% (64 to 99.8% CI

PPV= 97% 85% to 99.5%

NPV= 31% , 26 to 38%

Table 4—Accuracy of Increase in APS and APACHE III-Predicted Mortality in Predicting 100-Day Mortality Rate*

Variables	APS	Predicted Mortality
Sensitivity	15.3 (11.1–20.7)	63.9 (57.3–70.0)
Specificity	98.8 (93.7–99.8)	61.6 (51.1–71.2)
Positive predictive value	97.1 (85.1–99.5)	80.7 (74.1–85.9)
Negative predictive value	31.7 (26.4–37.5)	40.5 (32.4–49.0)

*Data are presented as % (95% confidence interval).

Scores and End of Life Care; PIC

Identifying potentially ineffective care in a community hospital*

Bruce M. Fleegler, MD; Donna K. Jackson, RN, MSN; Jim Turnbull, PhD; Charlene Honeycutt, RN, MBA; Carlos Azola, MS; Carl A. Sirio, MD

Table 3. Statistical analysis of derived equations for each study year, %

	1995 Point Estimate	1995 Confidence Interval, 95%	1996 Point Estimate	1996 Confidence Interval, 95%
Specificity	99.1	98.0–100	98.2	96.8–99.6
Sensitivity	42.0	33.9–50.0	28.7	22.8–34.6
Rate of false-positives	4.8	0.0–10.0	8.6	2.0–15.1
Positive predictive value	95.2	90.0–100.0	91.4	91.4–84.9

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 w/in 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 comatose 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

clinical investigations in critical care

Community-Wide Assessment of Intensive Care Outcomes Using a Physiologically Based Prognostic Measure*

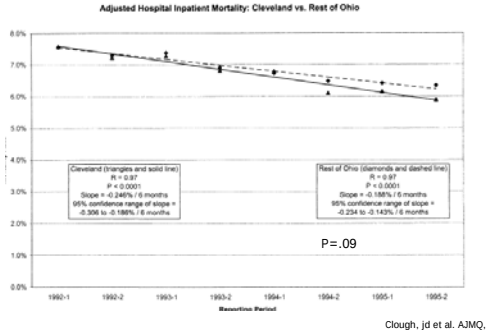
Implications for Critical Care Delivery From Cleveland Health Quality Choice

Carl A. Sirio, MD; Laura B. Shepardson, MS; Armando J. Rotondi, PhD; Greg S. Cooper, MD; Derek C. Angus, MB, CSB, MPH, FCCP; Dwain L. Harper, DO; and Gary E. Rosenthal, MD

FIGURE 3. Variation in SMRs (ie, observed/predicted hospital mortality) across hospitals. Error bars indicate 95% confidence intervals. SMRs > 1.0 indicate higher than expected mortality, while SMRs < 1.0 indicate lower than expected mortality. Major teaching hospitals are denoted by the black squares.

FIGURE 2. Differences in observed and predicted death rates across deciles of increasing risk, based on risk predictions from (top, A) the APACHE III national normative model[16] and (bottom, B) the locally derived model (see "Materials and Methods" section). Top, A: observed and predicted death rates differed ($p < 0.05$) in all deciles except for deciles 9 and 10. Bottom, B: observed and predicted death rates were similar ($p \geq 0.05$) in all deciles.

Do Reports of ICU Scores modify outcomes over time: CHQC



Clough, jd et al. AJMQ, 2002

Reaction to Poor Performance; CHQC

“Operation That Rated Hospitals Was Success, But the Patient Died”

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

The Wall Street Journal Aug. 23rd, 1999.

Pitfalls in Scoring Systems; Changes in Diseases & Medical Care

Intensive care unit length of stay: Recent changes and future challenges

Andrew L. Rosenberg, MD; Jack E. Zimmerman, MD, FCCM; Carlos Alzola, MS; Elizabeth A. Draper, MS; William A. Knaus, MD

Table 3. Observed and predicted intensive care unit (ICU) length of stay for the 15 most frequent nonoperative intensive care admission diagnoses among 38,888 patients studied in 1993–1996

ICU Admission Diagnosis	No. of Patients	Mean ICU Length of Stay (days*) Observed	Predicted	Paired t-Test	p Value
Acute myocardial infarction and unstable angina	5646	3.4	4.3	26.19	<.001
Congestive heart failure	1733	4.4	4.4	0.69	.490
Gastrointestinal bleeding due to ulcer or laceration	1463	3.8	3.8	0.26	.795
Bacterial or viral pneumonia	1045	7.5	6.8	2.90	.004
Drug overdose	1033	2.7	2.6	0.68	.494
Cardiac rhythm disturbance	959	3.4	3.8	3.87	<.001
Multiple trauma (excluding head injury)	883	5.2	4.8	1.53	.128
Head trauma (with or without multiple trauma)	882	5.3	5.5	0.70	.484
Sepsis (other than urinary tract)	798	6.8	7.1	1.13	.258
Stroke	614	4.8	4.3	2.86	.005
Cardiac arrest	570	5.3	5.7	1.69	.092
Respiratory arrest	565	6.8	6.8	0.02	.984
Diabetic ketoacidosis	504	3.3	2.9	2.42	.016
Gastrointestinal bleeding (diverticulosis or angiodysplasia)	469	3.5	3.7	1.12	.262
Subarachnoid hemorrhage or epidural/subdural hematoma	453	7.6	6.4	3.57	<.001

Lead-Time Bias in ICU Models

ARTICLE

Accepting Critically Ill Transfer Patients: Adverse Effect on a Referral Center's Outcome and Benchmark Measures

ARTICLE | Accepting Critically Ill Transfer Patients

Table 3. Intensive Care Unit and Hospital Outcomes for Patients Transferred from Another Hospital to the Medical Intensive Care Unit Compared with Direct and Combined Direct and Floor Intensive Care Unit Admissions, Adjusting for Case Mix and Physiologic Illness Severity*

Variable	Unadjusted	Partial Adjustment†	Full Case-Mix and Severity Adjustment‡	P Value
Increase in MICU length of stay, %				
Transfer vs. direct	51 (46–59)	40 (34–46)	38 (32–45)	<0.001
Transfer vs. (direct and floor)	18 (30–41)	16 (27–39)	16 (26–37)	
Increase in hospital length of stay, %				
Transfer vs. direct	48 (41–55)	41 (34–48)	41 (34–50)	<0.001
Transfer vs. (direct and floor)	4 (2–15)	7 (0.97–13)	3 (0.98–12)	
Odds ratio for hospital mortality				
Transfer vs. direct	2.5 (2.1–3.1)	2.5 (2.0–3.1)	2.2 (1.7–2.8)	<0.001
Transfer vs. (direct and floor)	1.4 (1.2–1.7)	1.6 (1.3–1.9)	1.5 (1.2–1.8)	
Odds ratio for MICU mortality				
Transfer vs. direct	2.4 (1.9–3.0)	2.3 (1.8–2.9)	2.0 (1.5–2.6)	<0.001
Transfer vs. (direct and floor)	1.5 (1.2–1.8)	1.7 (1.4–2.0)	1.6 (1.3–2.0)	
Odds ratio for MICU readmission				
Transfer vs. direct	1.9 (1.4–2.6)	1.9 (1.4–2.6)	1.8 (1.3–2.4)	<0.001
Transfer vs. (direct and floor)	1.2 (0.96–1.6)	1.1 (1.01–1.04)	1.3 (0.9–16)	

* Values in parentheses are 95% CIs. MICU = medical intensive care unit.
† Adjusted for age, sex, comorbid conditions, and diagnoses. This traditional adjustment is similar to or even more precise than many general hospital case-mix and severity adjustment methods that rely on administratively derived diagnosis-related group information.
‡ Adjusted for age, sex, comorbid conditions, diagnoses, and Acute Physiology Score.

Value of ICU Scoring Systems

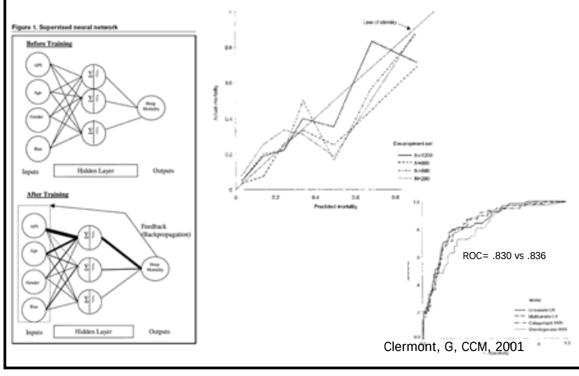
- *ICU Administrative resource;*
  - *Tool to quantify severity of illness & Case Mix*
  - *Changes in ICU ‘epidemiology’*
  - *Monitor outcomes when changing clinical/admin processes*
- *Compare and ICU’s performance over time*
  - *Adjusting to national ‘norms’*
  - *Adjusting to standard physiologic/organ fxn 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

Table 1. New methods to better mimic biologic processes and improve outcome prediction

Discipline	Technique	Description	Potential application in critical care
Biostatistics	Gray’s survival model [4,5]	A survival model that, unlike Cox modeling, accounts for hazards that are nonproportional over time.	Modeling survival after severe sepsis, where the impact of risk factors for death, such as age, comorbidity, and severity of illness, change over time [6].
Mathematics	Ordinary differential equations	A series of differential equations that describe the sequential change in the states of the components of the system over time.	Modeling the acute inflammatory response in sepsis to produce a “virtual organism” that can be used to run in silico (computer-generated) clinical trials [7].
Physiology	Power spectrum analysis	The mathematical transformation of digital data such that the entire waveform is represented as the sum of periodic (sine) waves of predefined frequency. The readout, which displays the relative contributions of each frequency, is called a power spectrum plot.	Analyzing heart rate variability in critical illness, which may provide caregivers with additional information about patient status, effects of interventions, and prognosis [8].
Molecular genetics	DNA microarray technology	A method that allows for the rapid analysis of large numbers of DNA alleles at the same time.	Identifying genetic polymorphisms associated with increased mortality in severe sepsis with the goal of tailoring drug selection and dosage and outcome prediction by correlating genetic profile with disease presentation [9].
Industrial engineering	Discrete events simulation	A technique that enables modeling of the competition of resources and the resulting queues, with changes occurring after specific events occur.	Planning critical care bed capacity to avoid inadequate or excess capacity [10].

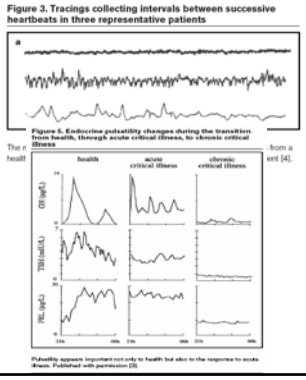
Improving Performance; Neural Networks

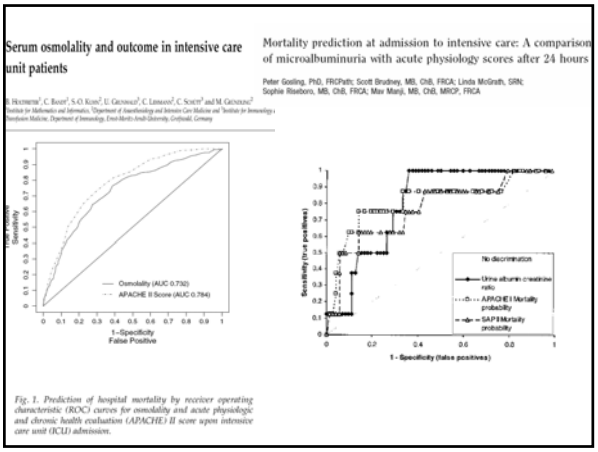


Clermont, G, CCM, 2001

Additional Data to enhance Models

- *Markers of inflammation*
  - *Serum amyloid A*
  - *Phospholipase A2*
  - *Neutrophil elastase*
  - *C-reactive protein*
  - *Interleukin 6 {failure to decrease from day0 to 4*
  - *Interleukin 6/10 ratios*
  - *TNF-alpha*
  - *Soluable 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?

Todd Dorman, M.D., FCCM
Johns Hopkins Medical Institutions
Baltimore, Maryland

Process versus Outcomes

Todd Dorman MD, FCCM
Associate Dean & Director, CME
Professor, Departments of Anes/CCM, Medicine, Surgery & The School of Nursing
Vice Chair Critical Care

Disclosures

I have no relevant financial interest to disclose

The Answer is Both!

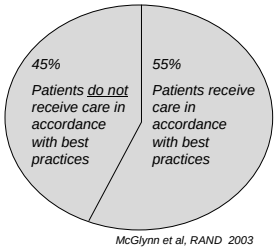
A Balanced Approach

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

Using recommended guidelines would help avoid harmful consequences:

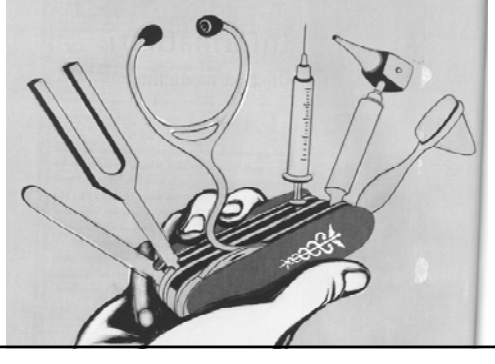
Hypertension	*68,000 avoidable deaths*
Heart Attack	*37,000 avoidable deaths*
Pneumonia	*10,000 avoidable deaths*
Colorectal cancer	*9,600 avoidable deaths*

Woolf, SH JAMA 1999



McGlynn et al, RAND 2003

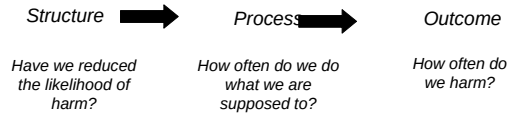
Why not use the right tool?



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



Have we reduced the likelihood of harm?

How often do we do what we are supposed to?

How often do we harm?

Adapted from Donebedian

Examples

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*

Structure

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

Process versus Outcome

- *Process*
- *Outcome*

Additional Suggested Readings

•Rubin, Pronovost, Diette. Advantages & disadvantages of process-based measures of health care quality. Int'l J Qual Health Care 2001. 13;469-474

•Mant J. Process versus outcome indicators in the assessment of quality of health care Int'l J Qual Health Care 2001. 13;475-480

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*

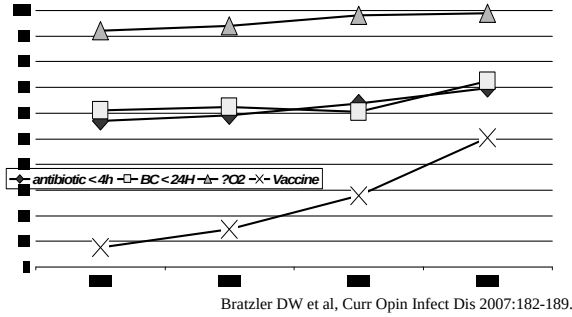
Why are you in healthcare?

- *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

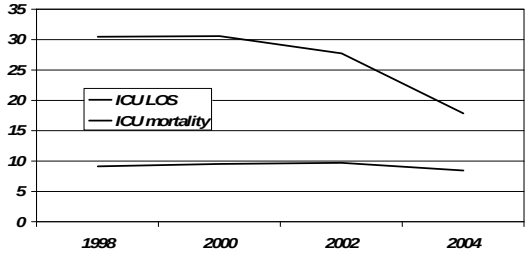
- *Evidence to guide our practice*
- *Impact on morbidity and mortality*
- *Variation in practice*
- *Must be able to change practice*

Pneumonia Processes Improved



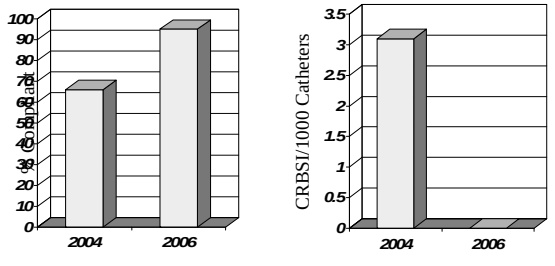
Bratzler DW et al, Curr Opin Infect Dis 2007:182-189.

Outcomes Improved



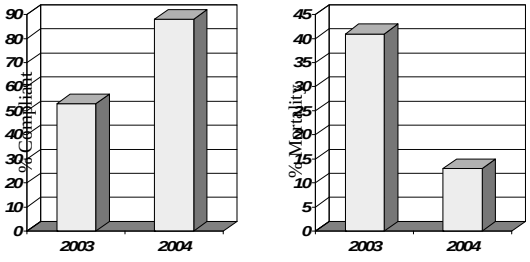
Bratzler DW et al, Curr Opin Infect Dis 2007:182-189.

CRBSI Process & Outcomes



Keystone Project: >100 ICUs in Michigan

Sepsis Bundle



VHA TICU 3 Project: 19 ICUs

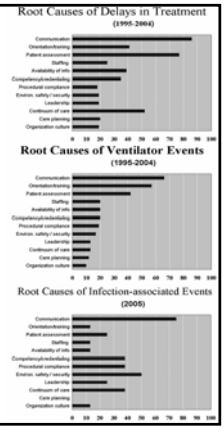
Wake Up

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

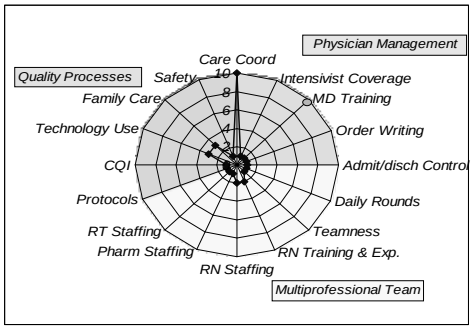
Ely EW et al, Intensive Care Med 1999:581-7.

Data Presentation: Dashboards

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



Integrated Data Presentation

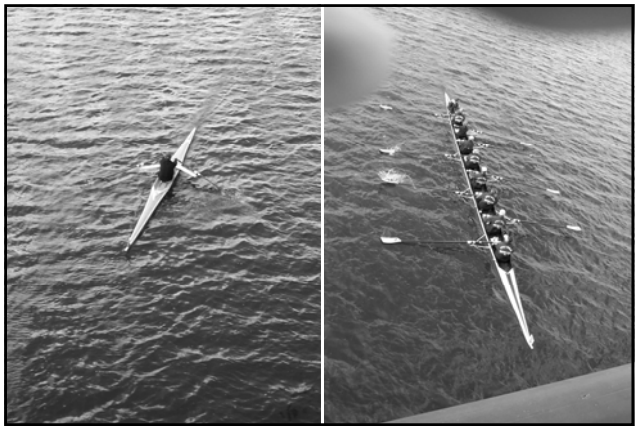


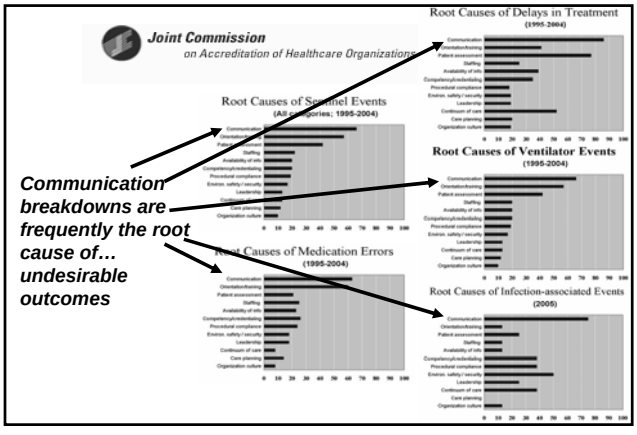
Is there a common problem?

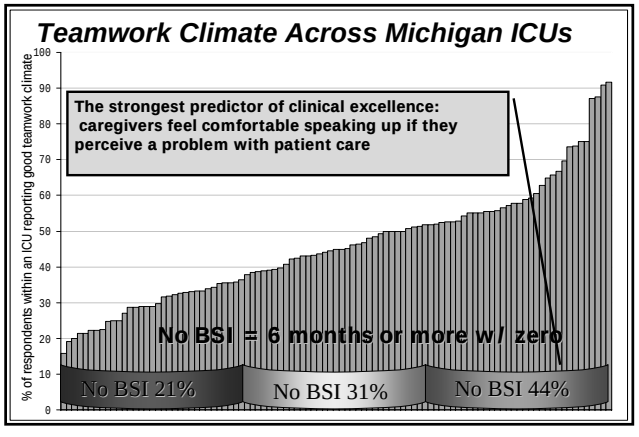
- *Is there a single thing or a small set of circumstances behind many of the errors/events that negatively impact patient care and outcome?*

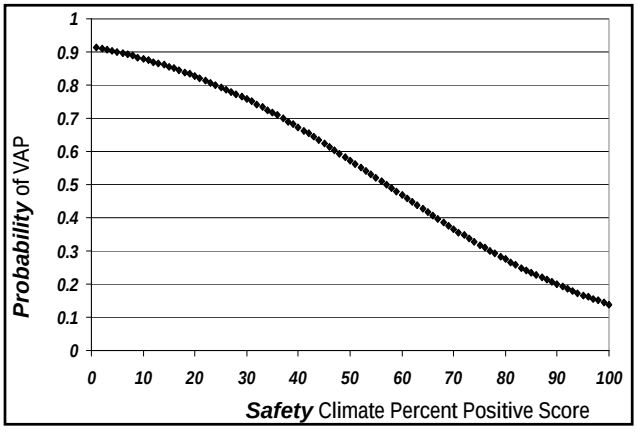
If there is it is……..

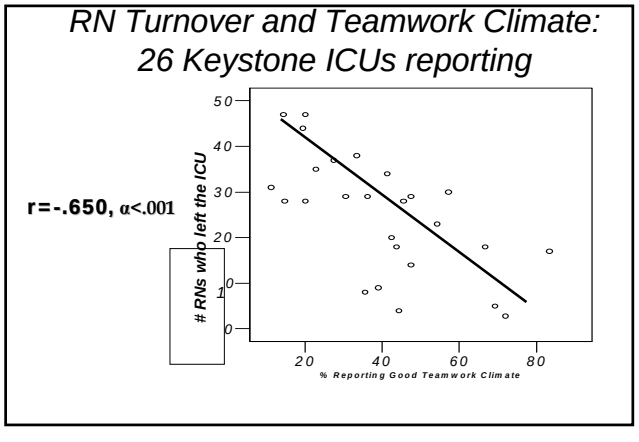
COMMUNICATION











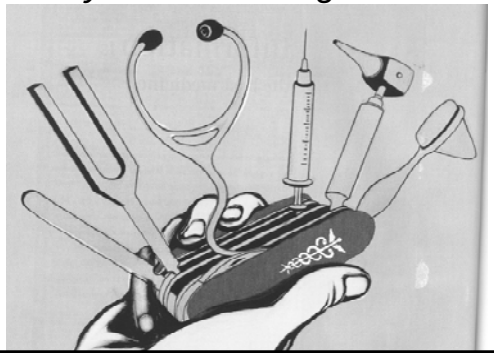
INCU

Intensive Nursing Care Unit

ITCU

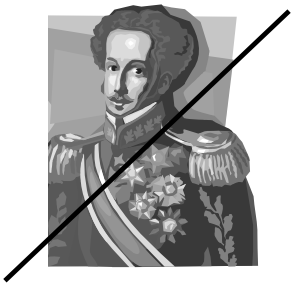
Intensive Team Care Unit

Why not use the right tool?

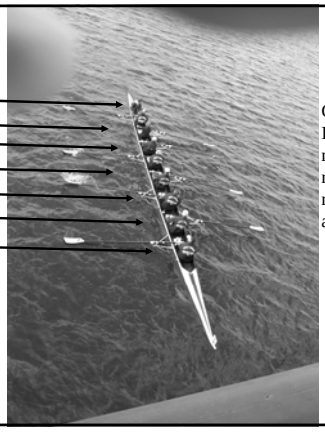


A Balanced Scorecard

The Intensivist's Role



The Intensivist's Role



I Have Protocols, So Why Do I Need a Closed Unit?

Hilmar Burchardi, M.D., F.R.C.A.
Georg-August University
Goettingen, Germany

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 (*Off 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).

Correspondence:
Prof. Dr. med. Hilmar Burchardi, FRCA
Kiefernweg 2
D-37120 Bovenden, Germany
Tel.: 0551-3813-678
Fax: 0551-3813-313
e-mail: hburcha@gwdg.de

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Interactive Clinical Forum

Avery Tung, M.D. Moderator

Discussants:
M.F. O'Connor, M.D.
A. Shander, M.D.
M. Avidan, MBBCh, DA, FCA
A. Friedrich, M.D.

A 59 yr F 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. SpO_2 on RA was 93%. BMI = 30 (86kg, 5'5") with mild ascites on CT scan. Hct 41%, Cr 1.2, HCO_3 = 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% FiO_2

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 H_20. BE = -5, Hct = 28, HCO_3 = 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?**

1. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med. 1999 Dec 9;341(24):1789-94.

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Perioperative beta-blocker therapy and mortality after major noncardiac surgery.
N Engl J Med. 2005 Jul 28;353(4):349-61

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

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

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-1308

2. Eichacker PQ, Gerstenberger EP, Banks SM, Cui X, Natanson C. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes.
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Anesthesiology. 2007 Jun;106(6):1226-31

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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?**

1. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G.
Colloids versus crystalloids for fluid resuscitation in critically ill patients.
Cochrane Database Syst Rev. 2004 Oct 18;(4):CD000567.

2. Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials.
Crit Care Med. 2004 Oct;32(10):2029-38.

3. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR.
A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury.
Crit Care Med. 2005 Aug;33(8):1681-7

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**

1. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators.
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Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury.
N Engl J Med. 2006 May 25;354(21):2213-24.

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Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery.

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A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients.
N Engl J Med. 2003 Jan 2;348(1):5-14.

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?

1. Corwin HL, Gettinger A, Fabian TC, May A, Pearl RG, Heard S, An R, Bowers PJ, Burton P, Klausner MA, Corwin MJ; EPO Critical Care Trials Group.
Efficacy and safety of epoetin alfa in critically ill patients.
N Engl J Med. 2007 Sep 6;357(10):965-76

2. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group.
N Engl J Med. 1999 Feb 11;340(6):409-17

3. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM.
Blood transfusion in elderly patients with acute myocardial infarction.
N Engl J Med. 2001 Oct 25;345(17):1230-6.

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?

1. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients.
N Engl J Med. 2001 Nov 8;345(19):1359-67

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Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial.
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Resistant Infections in the ICU: What Can/Should the Intensivist Do?
Antibiotic Resistance

Michael S. Avidan, M.B., B.Ch.
Washington University
St Louis, Missouri

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:

Date	Event
1675	Antony **van Leeuwenhoek** discovered bacteria.
1796	Edward **Jenner** laid the foundation for vaccines.
1848	Ignaz **Semmelweis** discovered hand washing could prevent infection or contagion.
1857	Louis **Pasteur** introduced the germ theory of disease.
1867	Joseph **Lister** pioneered antiseptics during surgery.
1876	Robert **Koch**, by studying anthrax, showed the role of bacteria in disease. Dmitri **Ivanovski** discovered viruses.
1892	Alexander **Fleming** discovered penicillin.
1928	Jonas **Salk** developed polio vaccine.
1955	Luc **Montagnier** and Robert **Gallo** identified the virus that causes AIDS.
1983	

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.[1] 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.[2] 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.[2] 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.[2] 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.*[3]

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.[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]

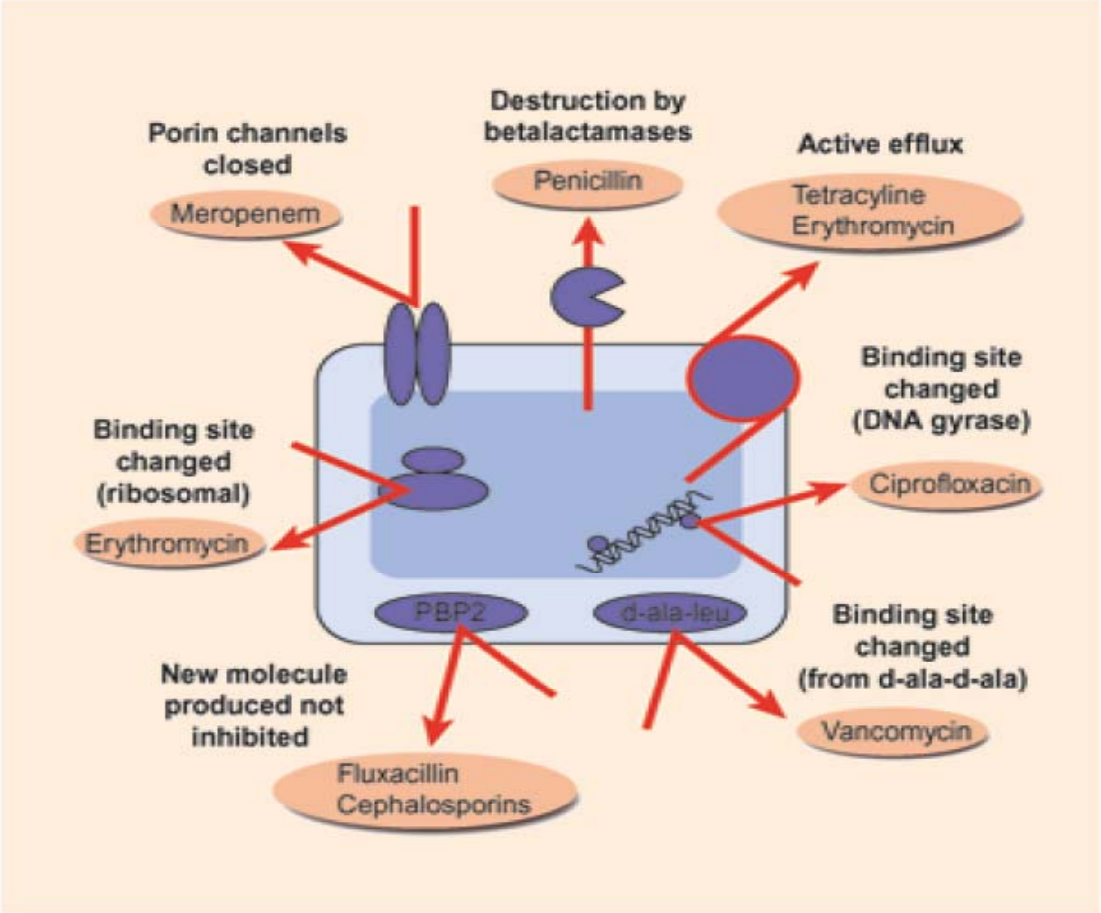

Figure 1: Mechanisms of Antibiotic Resistance

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)[7], exploiting plants and the ocean, anti-adhesin

approaches, and riboswitches. 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.[8] 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.[8] Anti-adhesin strategies may prevent bacteria from binding to host surface receptors thereby rending 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.[9] Blocking riboswitch binding could halt the expression of essential genes.[9]

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/

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Sepsis: What's New in Basic Science Update

Judith Hellman, M.D.
Massachusetts General Hospital
Boston, Massachusetts

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.

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

Pro

Geoffrey K. Lighthall, M.D., Ph.D.
VAMC
Palo Alto, California

Con

Michael F. O'Connor, M.D.
University of Chicago
Chicago, Illinois

NOTES

Sepsis: What's New in Clinical Management

Vivek K. Moitra, M.D.
Columbia University
New York, New York

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