Chapter 30

Evidence-Based Medicine in the Intensive Care Unit

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Introduction

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best-available external clinical evidence from systematic research [1]. EBM asks questions, finds and appraises the relevant data, and uses that information for everyday clinical practice. This is done by formulating a clear clinical question from a patient's problem, searching the literature for relevant clinical articles, evaluating the evidence for its validity and usefulness, and then implementing useful findings into clinical practice.

The central pillar of EBM is the randomized controlled trial (RCT), defined as a clinical trial that involves at least one test treatment and one control treatment, concurrent enrollment and follow-up of the test- and control-treated groups, and in which the treatments to be administered are selected by a random process, such as the use of a random-numbers table. However, often sample sizes are too small to assess endpoints such as mortality and then one needs a systematic review of the literature and a meta-analysis using quantitative methods.

The outcome of these processes enables the evidence to be classified into five levels and this subsequently facilitates the development of five grades of recommendations with regard to treatment options. For a maneuvre to receive a grade A recommendation it needs at least two studies providing level 1 evidence supporting the intervention. Large prospective RCTs with unequivocal results and a very low risk of bias or a meta-analysis with low risk of bias provide level 1 evidence. In contrast non-randomized and historically controlled studies as well as case reports, uncontrolled studies, and expert opinion are classified as level 4 and 5 evidence, allowing only a grade E recommendation.

We screened the intensive care unit (ICU) literature using these EBM principles for maneuvres that may impact on infectious morbidity and mortality. We have classified the most common maneuvres according to levels of evidence and grades of recommendations (Table 1).

Table 1. Levels of evidence and grades of recommendations

Level	Description
1	Large prospective randomized controlled clinical trial with unequivocal results and very low risk of bias; A meta-analysis with a low risk of bias
2	Small prospective randomized controlled clinical trial with unclear results and moderate to high risk of bias; A meta-analysis with a moderate to high risk of bias
3	A prospective randomized controlled clinical trial but not performed in the appropriate patient group; A non-randomized but controlled clinical trial in the correct patient population Cohort studies and patient controlled studies
4	A non-randomized and historically controlled study
5	Case reports Uncontrolled studies Expert opinion
Grade	**Description**
A	A maneuvre can be recommended if supported by at least two level 1 studies
B	A maneuvre can be recommended if supported by one level 1 study
C	A maneuvre can be recommended if supported only be level 2 studies
D	Supported by at least one level 3 study
E	Only supported by studies rated at level 4 and 5

The Five Traditional Infection Control Maneuvres

Hand Washing, Isolation, Protective Clothing, Care of Equipment and Environment

Hand hygiene has never been shown to control pneumonia or reduce mortality in ventilated patients in a randomized trial. The efficacy of hand hygiene in reducing the incidence of infection has been studied in six non-randomized and two randomized trials [2–9] (Table 2). In only four of these studies was

Table 2. Studies into the effect of hand hygiene on the incidence of nosocomial infections including pneumonia

Author	Year	Study design	Endpoint	Outcome: infectious morbidity	Evidence
Casewell and [2] Phillips	1977	Sequential	Patients with *Klebsiella*	Significant reduction in patients carriers and infected with *Klebsiella* Effect on pneumonia not mentioned	Level 4
Massanari and [3] Hierholzer	1984	Cross-over	Overall infections	Significant reduction of nosocomial infection on some ICUs. Effect on pneumonia not mentioned	Level 4
Maki [4]	1989	Sequential, comparative	Overall infections	Significant reduction of nosocomial infection on some ICUs. Effect on pneumonia not mentioned	Level 4
Simmons et al. [5]	1990	Prospective, retrospective control	Infected patients	No effect on pneumonia	Level 4
Doebbeling [6] et al.	1992	Cross-over	Infected patients	Significant reduction of nosocomial infection on some ICUs. No effect on pneumonia	Level 4
Webster et al. [7]	1994	Sequential	MRSA carriage	Control of MRSA outbreak. Significant reduction of nosocomial infections	Level 4
Koss et al. [8]	2001	RCT	Patients with pneumonia	No effect on pneumonia	Level 2
Slota et al.[9]	2001	RCT	Infected patients	No difference	Level 2

RCT, randomized controlled trial

pneumonia the endpoint and in none did hand washing have any impact. The only study that demonstrated an impact on mortality of hand hygiene was the cohort study of Semmelweis in 1861 [10]. This classic study showed the survival benefit of hand disinfection. In women admitted for delivery, the mortality from child bed fever was significantly reduced from 11.40% to 3.04 % following the implementation of hand washing with chlorinated lime, compared with an historical control group of doctors who did not wash their hands. This study is often referred to as the prime evidence for the effectiveness of hand disinfection. The recent experience with the corona virus infection causing severe acute respiratory syndrome (SARS) in Toronto demonstrates that rigorous implementation of the traditional infection control measures can control an outbreak of a high-level pathogen similar to *Streptococcus pyogenes* seen 150 years ago in Vienna [11].

There are no data available on the effect of isolation, protective clothing, care of equipment, and environment on the rate of bacterial pneumonia and the associated mortality in ventilated patients.

The five traditional infection control measures target the control of transmission of micro-organisms via the hands of carriers. They are important but their impact should not be overestimated. An optimal infection control policy can only reduce infections due to micro-organisms acquired on the unit, i.e., secondary endogenous and exogenous infections. They fail to influence primary endogenous infections due to micro-organisms present in the admission flora. This type of infection is the major infection problem on the ICU varying between 60% and 85% (Chapter 5).

Non-Antibiotic Interventions as Infection Control Maneuvres

Positional therapy. Severely ill patients who require ventilation are often treated in the supine position. This leads to segmental collapse, basal atelectasis, and impaired clearance of secretions. These factors increase the risk of pneumonia. Treating a patient in a specialized rotating bed in which the patient is continuously rotated from -40° +40° around their longitudinal axis could theoretically help in the prevention of pneumonia.

There is one positive meta-analysis of six RCTs [12–14] showing a significant reduction in pneumonia in patients who received rotational therapy, thereby supporting kinetic therapy as an infection control maneuvre. Of the six studies, five were performed in surgical or neurological patients. The sixth trial in which there was no reduction in pneumonia was performed in non-surgical ICU patients. A further more recent RCT in a mixed ICU population does not support the conclusion of the meta-analysis. Rotation therapy requires special beds, which may be associated with increased costs.

Semi-recumbent position. Although in general the throat has been considered as the internal source of potential pathogenic micro-organisms (PPM) causing pneumonia, some people believe that aspiration of PPM carried in the stomach may play a role in the pathogenesis of pneumonia, the so-called stomach-lung route [15]. Based upon this concept, ventilating patients in a semi-recumbent position is thought to have a beneficial effect on reducing the incidence of reflux and aspiration from the stomach, whereby pneumonia in ventilated patients could be prevented. This maneuvre has been investigated in two RCTs [16, 17] (Table 3). The first study shows that ventilating patients in a semi-recumbent position leads to a significant reduction in pneumonia. Mortality rates, however, were identical in both test and control group. However, patients who underwent abdominal or neurosurgery, patients with refractory shock, and patients who were readmitted to ICU within 1 month were excluded. The second RCT, only published in abstract form, failed to confirm these results. There was no difference in pneumonia rate or mortality.

Sub-glottic drainage. Stasis of saliva contaminated with potential pathogens above the cuff of the endotracheal tube increases the risk of aspiration pneumonia. The removal and prevention of this salivary stasis using continuous aspiration via a specially designed endotracheal tube is thought to prevent pneumonia. The intervention of sub-glottic drainage has been evaluated in four RCTs [18–21] (Table 3). Three studies were performed in a mixed ICU population requiring ventilation for >72 h and the fourth study in cardiac surgery patients. The results of these trials are not consistent. Two studies showed a significant reduction in pneumonia, the other two failed to show any impact on pneumonia during ventilation. A meta-analysis of the four studies shows a significantly reduced relative risk of pneumonia due to sub-glottic drainage [relative risk (RR) 0.49 (0.39–0.73)]. There was no difference in mortality in test and control groups in any of the studies. Although the specially designed tubes and suction equipment are expensive, this technique has been suggested to be cost effective on theoretical grounds only [22]. Recent work indicates that sub-glottic drainage causes severe tracheal mucosal damage at the level of the suction port [23].

Immunomodulation

Enteral feeding. Total parenteral nutrition has been shown to be harmful in terms of higher infection rates and liver impairment [24, 25]. This prompted the desire to enterally feed the ICU patient as quickly as possible because it is thought to be essential for the gut anatomy and physiology, in order to prevent loss of mucosa integrity and subsequent translocation. In addition, several nutrients added to the enteral feed have been shown to influence immunologi-

Table 3. Randomized controlled trials into the effect of non-antibiotic interventions on the pneumonia rate and mortality in ventilated patients. RCT=randomised controlled trial; RR=relative risk (95% confidence intervals)

Maneuvre	Author	Year	Study design	n	Pneumonia	Mortality	Evidence
Rotation therapy	Choi and Nelson [12]	1992	Meta-analysis of 6 studies	419	RR 0.50 p=0.002	No difference	Level 1
	Traver et al. [14]	1995	RCT	103	RR 0.62 p=0.21	RR 0.62 p=0.21	Level 1
Semi-recumbent position	Drakulovic et al. [16]	1999	RCT	86	RR 0.24 p=0.003	RR 0.62 p=0.21	Level 1
	Van Nieuwen -hoven et al. [17]	2002	RCT	221		No difference	Level 1
Subglottic suction drainage	Mahul et al.[18]	1992	RCT	145	RR 0.46 (0.23-0.93)	RR 1.14 (0.62-2.07)	Level 1
	Valles et al. [19]	1995	RCT	190	RR 0.56 (0.31-1.01)	RR 1.07 (0.70-1.65)	Level 1
	Kollef et al. [20]	1999	RCT	343	RR 0.61 (0.27-1.40)	RR 0.86 (0.30-2.42)	Level 1
	Smulders et al. [21]	2002	RCT	150	RR 0.25 (0.07-0.85)	RR 1.2 (0.55-2.61)	Level 1

cal and inflammatory responses in humans. There are two recent meta-analyses on immunonutrition in the critically ill [26, 27] (Table 4). Both show a significant reduction in overall infection rates, although they do not specifically consider pneumonia. There was no reduction in mortality in either of the meta-analyses. Surgical patients seemed to benefit more than medical. In two more recent large RCTs, mortality rates were significantly higher in the subgroup that received immunonutrition. Some have speculated that added arginine might have been detrimental to the immune system [28, 29].

Steroids. High doses of steroids given to septic patients are thought to be beneficial for three reasons [30–34]. Steroids effectively suppress generalized inflammation due to micro-organisms and their toxins. They have been shown to significantly reduce septic shock and early mortality within 72 h. They significantly reduce mortality caused by particular invasive infections, including meningitis, typhoid, and *Pneumocystis carinii* pneumonia. The major perceived side effects of high-dose steroids are the associated immune suppression and subsequent risk of super-infections. Indeed the two meta-analyses show a trend towards increased mortality from secondary infection in patients receiving steroids [30, 31]. The next logical step would be to combine steroids with selective decontamination of the digestive tract (SDD), whereby the perceived harmful effects of steroids could be abolished. In that way the early survival benefit from steroids could be preserved by keeping the patient free from secondary infections using SDD.

Anti-inflammatory mediators. Almost 60 RCTs have tested the hypothesis that modulation of the endogenous host inflammatory response can improve survival for patients with a clinical diagnosis of sepsis. The results have been frustrating and no new agent has been introduced into clinical practice [35].

Pooled data from studies using a monoclonal antibody to neutralize tumour necrosis factor demonstrate a statistically significant 3.5% reduction in mortality. In aggregate, the three completed studies using recombinant interleukin-1 (IL-1) receptor antagonists to neutralize IL-1 also showed an absolute mortality reduction of 5%. Zeni et al. [36] showed that the combined results of all completed trials, independent of the therapeutic agents employed, demonstrate a statistically significant 3% overall reduction in 28-day all-cause mortality. It is questionable whether this small clinical benefit is sufficiently important to justify clinical use of these therapies, given the costs and potential toxicity of the agents involved.

Immunoglobulins. Polyclonal intravenous immunoglobulins (IVIG) significantly reduce mortality and can be used as an extra treatment option for sepsis and septic shock [37]. Overall mortality was reduced in patients who received polyclonal IVIG [n=492, RR=0.64, 95% confidence interval (CI) 0.51–0.80]. For the

Table 4. Randomized controlled trials into the effect of non-antibiotic interventions on the general infection rate and mortality in ventilated patients. RCT=randomized controlled trial; RR=relative risk (95% confidence intervals)

Maneuvre	Author	Year	Study design	*n*	Infection rate	Mortality	Evidence
Immunonutrition	Beale et al. [26]	1999	Meta-analysis of 12 studies	1482	RR 0.67 (0.50-0.89) p=0.006	RR 0.05 (0.78-1.41) p=0.76	Level 1
	Heyland et al. [27]	2001	Meta-analysis of 22 studies	2419	RR 0.66 (0.54-0.80)	RR 1.1 (0.93-1.31)	Level 1
Steroids	Cronin et al. [30]	1995	Meta-analysis o of 9 RCTs	1232	No difference	RR 1.13 (0.99-1.29)	Level 1
	Lefering and Neugebauer [31]	1995	Meta-analysis of 10 RCTs	1329	No difference	Difference in mortality -0.2% (-9.2 - 8.8)	Level 1
	Bollaert et al. [32]	1998	RCT	41	No difference	Difference in mortality 31% (1-61)	Level 1
	Briegel et al. [33]	1999	RCT	40	No difference	No difference	Level 1
	Annane et al. [34]	2002	RCT	300	No difference	Significant reduction	Level 1

two high-quality trials on polyclonal IVIG the RR for overall mortality was 0.30, but the CI was wide (95% CI 0.09–0.99, n=91). However, all the trials were small and the totality of the evidence is insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal IVIG remains experimental. This is level 2 evidence prompting a grade C recommendation for usage.

Activated protein C. Drotrecogin α (activated), or recombinant human activated protein C, is thought to have anti-inflammatory, anti-thrombotic, and profibrinolytic properties. There is one large RCT of 1,690 patients in which the mortally rate was 30.8% in the placebo group and 24.7% in the drotrecogin α group. This translates into an absolute reduction in risk of death of 6.2% (P=0.05). The incidence of serious bleeding was higher in the drotrecogin α (activated) group than the placebo group [38]. This is level 1 evidence and grade B recommendation.

Low Tidal Volume

An RCT of 861 patients concluded that by using lower tidal volumes (6 ml/kg) during mechanical ventilation compared with traditional tidal volumes (12 ml/kg) mortality was lower (31.0% vs. 39.8%, P=0.007) [39]. This is an absolute mortality reduction of 8.8% (95% CI 2.4–15.3) and 11 patients need to receive low tidal volume ventilation to save 1 life.

Glucose Control

In 1,548 patients, intensive insulin therapy reduced mortality during intensive care from 8.0% to 4.6% (P<0.04) [40]. When blood glucose levels were maintained below 6.1 mmol/l, there was an absolute mortality reduction of 3.7% (95% CI 1.3–6.1), which translates into 27 patients needing insulin therapy to prevent 1 death (Table 5).

Table 5. Effect of intervention on reduction in mortality

Intervention	Relative risk [95% CI]	Absolute mortality reduction [95% CI]	No. needed to treat	Grade of recommendation
Low tidal volume [39]	0.78 [0.65 to 0.93]	8.8 [2.4 to 15.3]	11	B
Activated protein C [38]	0.80 [0.69 to 0.94]	6.1 [1.92 to 10.4]	16	B
Intensive insulin [40]	0.40 [0.36 to 0.82]	3.7 [1.3 to 6.1]	27	B
Steroids [34]	0.90 [0.74 to 1.09]	6.4 [-4.8 to 17.6]	16	B
Selective decontamination [42]	0.65 [0.49 to 0.85]	8.1 [3.1 to 13.0]	12	A

Antibiotic Intervention

Selective decontamination of the digestive tract. The philosophy of SDD has been discussed in Chapters 9 and 14. The efficacy of SDD has been studied in 54 RCTs. There are nine meta-analyses of RCTs on SDD. All the meta-analyses show that rates of infection, particularly pneumonia, were significantly reduced. This was independent of the method used to diagnose pneumonia. The full four-component protocol of SDD in a mixed ICU population requiring a minimum of 72 h of ventilation has been analysed in 17 studies [41]. The application of the full four-component protocol reduces morbidity due to pneumonia by 65% and mortality by 22%.

In the latest SDD trial, the randomization was between ICUs and not patients as in all previous trials [42]. This study of approximately 1,000 patients is the largest single study yet undertaken. The primary endpoint was mortality as opposed to infectious morbidity. The risk of mortality was significantly reduced to 0.6 (0.4–0.8) in the unit where SDD was administered to all patients. In the previous 53 trials, the patient had been the 'randomization unit' therefore half the population in the respective ICUs was not decontaminated. Therefore it is possible that the control patients, although not receiving SDD, benefited from the intervention as they were exposed to a lower risk of microbial acquisition and carriage, infection, and subsequent mortality. This 'dilution risk' due to the control group being present with decontaminated patients at the same time in the same unit is termed 'contamination bias'. The design of the latest trial has avoided this type of bias and may explain the highest reported mortality reduction to date, an 8% absolute reduction in mortality. Recently a second RCT of large sample size found an identical 8% mortality reduction [43], meaning that only 12 patients need to receive SDD to prevent 1 death.

The main concern of the liberal use of antibiotics is the emergence of resistance. Antimicrobial resistance and subsequent super-infections emerge within 2 years of the launch of any new parenteral antibiotic [44]. When the enteral antibiotics polymyxin and tobramycin are added and successful decontamination achieved, organisms that may become resistant to the parenteral antibiotic in the gut are eradicated (Chapter 28). In the most recent meta-analysis of 36 trials comprising 6,922 patients covering a period of more than 15 years of clinical investigation, neither super-infections nor outbreaks with multi-resistant bacteria were observed [41]. The Agency for Health Research and Quality of the US Department for Health and Human Services reports that SDD using regular surveillance cultures and applying paste and suspension is cheap and easy to implement [45]. The cost-effectiveness of SDD is not properly assessed [46-49], but costs can hardly be a major concern for a maneuvre of 6 Euros a day that reduces pneumonia by 65 % and mortality by 22% without antimicrobial resistance emerging in unselected ICU patients.

Conclusion

Currently there are five maneuvres that control mortality, all published within the last 3 years, in the twenty-first century (Table 6). Four have been assessed in only one RCT in specific subsets. The only maneuvre with a Grade A recommendation from the Agency for Health Research and Quality of the US Department for Health and Human Services [45] that is applicable to all types of patients is SDD. In addition, only SDD controls resistance, which is becoming the major issue for this century.

Table 6. Analysis of the literature and grading of evidence, and recommendations for the control of morbidity and mortality due to infection in ventilated patients on ICU

	Reduced infection		Reduced mortality	
	Level of evidence	**Grade of recommendation**	**Level of evidence**	**Grade of recommendation**
Non-antibiotic interventions				
Handwashing/isolation/ protective clothing/ care of equipment and environment	5	E	4	E
Positioning				
Rotation therapy	none	none	none	none
Semi-recumbent position	none	none	none	none
Subglottic secretion drainage	none	none	none	none
Immunomodulation				
• Immunonutrition	1	A	none	none
• Steroids	none	none	1	B
• Immunoglobulins	none	none	2	C
• Activated protein-C	none	none	1	B
• Anti-inflammatory modulators	none	none	1	C
Low tidal volume	none	none	1	B
Intensive insulin	none	none	1	B
Antibiotic interventions *Selective Decontamination of Digestive tract (4 component)*	1	A	1	A

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