British Journal of Medicine & Medical Research
2(4): 636-646, 2012

SCIENCEDOMAIN *international*
www.sciencedomain.org

Costs of Additional Treatment Success (COATS) Based on Numbers Needed to Treat (NNT) is a Simplified Calculation Method to Facilitate Physicians Medical Decisions with Regards to Monetary Costs

Manfred Weiss[1*], Frank Grom[2] and Franz Porzsolt[2]

[1]Clinic of Anaesthesiology, University Hospital Medical School, 89070 Ulm, Germany.
[2]Clinical Economics, University of Ulm, 89075 Ulm, Germany.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MW, FG and FP participated in study conception, study design, data analysis, interpretation and drafting of the manuscript. All authors read and approved the final manuscript.

Research Article

Received 27th March 2012
Accepted 6th September 2012
Published 31st October 2012

ABSTRACT

Aims: Due to limited resources, to provide a simple and transparent tool for physicians to facilitate budget-related, medical decisions in any patient.
Study Design: Comparative study.
Methodology: Several articles with topics referring to the 2008 "Surviving Sepsis Campaign" guidelines in critically ill patients with varying effects on defined clinical endpoints were analyzed regarding the costs of additional treatment success (COATS). A simplified ICER = incremental cost-effectiveness ratio to assess COATS was expressed as the product of the number of patients needed to treat (NNT) and the difference in treatment costs per patient.
Results: In publications with significant treatment effects enabling calculation of NNTs, calculating "COATS = NNT x delta costs per patient", mean costs to avoid one additional death or morbidity could be defined. Considering the 95% confidence interval, estimated costs at minimum and maximum to reach distinct clinical endpoints could be expressed. In studies with no significant results, NNTs and COATS were tending to infinity.
Conclusion: COATS based on NNT as a simplified ICER is an easy way for the

**Corresponding author: Email: manfred.weiss@uni-ulm.de;*

physician at the bedside caring for individual patients to explicitly describe the amount of money which has to be spent to reach definable aims in the clinical setting in one additional patient, such as reduction of mortality or morbidity, or to reassess therapies without significant results. In contrast to COATS, ICER based on quality-adjusted life years may be necessary to perform calculation of the short-term and long-term costs for the community and the adequate allocation of health care resources.

Keywords: Budget-related decisions; costs; intensive care units; incremental cost-effectiveness ratio; morbidity; mortality; sepsis.

ABBREVIATIONS

APACHE II – Acute Physiology and Chronic Health Evaluation II score; ARR - absolute risk reduction; CER - control event rate; CIPNP - critical illness polyneuropathy; EER - experimental event rate; CI - confidence interval; COATS - costs of additional treatment success, i.e., NNT x costs per patient; CUA - cost-utility analysis; HTA - health technology assessment; ICU - intensive care unit; ICER - incremental cost-effectiveness ratio; IIT - intensive insulin therapy; MODS - multiple organ dysfunction syndrome; NHS - National Health Service; NNT - number needed to treat; rhAPC - recombinant human activated protein C; QALY - quality-adjusted life years; SSC - Surviving Sepsis Campaign; 95%CI - 95% confidence interval;

1. INTRODUCTION

In 2008, the update of the “Surviving Sepsis Campaign” (SSC) guidelines (Dellinger et al., 2004; Dellinger et al., 2008) has been published to provide recommendations for best current care directly targeting severe sepsis and general care of the critically ill patient. These guidelines intend to improve outcome (Dellinger et al., 2004; Dellinger et al., 2008). However, besides beneficial effects for patients, application of some guidelines may also lead to undesirable effects, such as harm to patients, more burdens on staff and patients, and enhanced costs. For example, the expensive application of recombinant human activated protein C (rhAPC) in septic shock may be a two-sided sword, reducing mortality on the one side but also increasing the economic risks on the other side (Dellinger et al., 2004; Dellinger et al., 2008).

In daily clinical work, physicians make decisions concerning own clinical experience and knowledge, recommendations of societies of their profession with evidence-based medicine guidelines, effects of interventions on morbidity and mortality and individual costs. Due to limited resources, physicians are confronted with the individual costs and the financial burden for societies. Thus, for physicians, simple tools for budget-related decisions based on clinical reasoning to facilitate clinical decision making and justification regarding different stakeholders of health care systems (patients, physicians, societies, lawyers, insurance companies, economists, politicians, health care providers and health care users) during daily clinical work are desirable. Physicians are aware of the costs per patient at least for expensive therapies, and they are used to read numbers needed to treat (NNTs) in scientific publications, and, thereby, can estimate effectiveness of treatment options.

Usually, an incremental cost-effectiveness ratio (ICER) is performed to assess costs of additional treatment success (COATS). ICER may reflect in a transparent form an assessment based on data but in a much less transparent form an appraisal based on

values, such as quality-adjusted life years (QALYs), which express a virtual figure which is based on somebody else's evaluation. The QALY is based on the number of years of life that would be added by the additional treatment. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death. If the extra years would not be lived in full health, for example if the patient would lose a limb, or be blind, have to use a wheelchair, or need chronic dialysis, then the extra life-years are given a value between 0 and 1 to account for this. ICER divides the difference in costs (f.e. for rhAPC (Moerer, Burchardi, 2006), € 7.400 – 0) by the difference in effects (f. e., QALYs or absolute risk reduction, ARR): ICER = Δ costs / Δ QALY, or ICER = Δ costs / ARR. ARR is defined as control event rate (CER) minus experimental event rate (EER). Thus, ICER = Δ costs / Δ (CER - EER). ICER to estimate costs per life year and costs per QALY from the perspective of third party payers, such as national health services and personal social services, include a wide range of variables, such as known patient benefits and harms, life expectancy, baseline risk, effectiveness data, health state value, resource use, short-term and long-term costs, future costs and future benefits (life years) (Green et al., 2006). Most of these data are not available for physicians at the bedside, and calculations much to complex to perform for them, to take them into account for budget-related decisions to reach distinct clinical endpoints such as lowering mortality or morbidity. Moreover, physicians are more used to deal with NNT than with ARR in scientific papers and in clinical decision making to reach specific aims and clinical endpoints. Since NNT = 1 / ARR, calculation of ICER can be simplified to ICER = Δ costs x NNT, which represents COATS. The NNT reflects the number of individuals who have to be treated to prevent one additional event in the experimental group as compared to the control group (Worster, Rowe, 2001). COATS based on data such as NNT is probably a more useful information for the physician at the bedside who has to decide based on her/his own evaluation under the aspect of limited resources and her/his budget than ICERs reflecting an appraisal based on values, such as QALYs.

Therefore, in the present paper, we suggest a simplified ICER based on data (NNT), that is the COATS, which is easy to understand and to apply for physicians in daily practice relating the solution of a clinical problem to the monetary costs. When the cost per patient is multiplied with the NNT to yield a distinct clinical endpoint, a simplified ICER results in an easy assessment of COATS. Moreover, physicians are interested to estimate the range of estimated costs at minimum and at maximum to reach distinct clinical endpoints. This can be expressed by including the 95% confidence interval (95% CI) of the NNT in the calculation of COATS.

Therefore, to make an example, present treatment recommendations for critically ill patients will be presented applying COATS to treatment options with clearly up to marginally beneficial effects on clinically endpoints, such as mortality or morbidity. Intensive-care units (ICUs) are the most expensive part of a hospital. Therefore, we decided to use treatment guidelines for critically ill patients on the ICU to demonstrate the usefulness of COATS for budget-related decision making for physicians. We will focus on COATS to estimate the range of costs of main treatment recommendations in different subgroups of critically ill patients regarding mortality and morbidity. We demonstrate that physicians may have to reassess therapies which are not supported by significant results regarding clinical endpoints with NNTs and COATS tending to infinity. We suggest to simplify ICER based on data (NNT) for physicians, that is COATS, to increase acceptance of cost-effectiveness analyses in their daily clinical work.

2. METHODOLOGY

2.1 Study Design

Publications of the reference list of the SSC 2008 guidelines were used and a Medline/PubMed research has been performed. To make an example for the simplified calculation method COATS, original studies and meta-analyses demonstrating clearly up to marginally beneficial effects on clinically endpoints, such as mortality or morbidity, were chosen. Papers revealing ARR, NNT with 95%CI, and costs per patient were used as a basis to calculate COATS. NNT was calculated as NNT = 1/ARR. 95%CI for ARR was calculated as 95%CI = ARR ± 1.96 x σ. The standard error σ was calculated as follows:

$$\sigma - \sqrt{\frac{p_1 \times (1-p_1)}{n_1} + \frac{p_2 \times (1-p_2)}{n_2}}$$

With n1 = number of patients in the control group, in which an event occurs r1-times, and n2 = number of patients in the intervention group with r2-times the event. This results in event rates of p1 = r1/n1 and p2 = r2/n2.

The costs per patient and COATS were calculated for the most relevant examples of treatment recommendations in the 2008 SSC guidelines which therefore have been listed in the management bundle which has to be fulfilled within the first 24 hours (Dellinger et al., 2004; Dellinger et al., 2008) for critically ill patients with severe sepsis / septic shock. These examples are the most common, most relevant and controversially discussed, and most expensive (rhAPC) treatment recommendations. The following treatments in patients with severe sepsis / septic shock served as examples: application of rhAPC (Bernard et al., 2001; Moerer and Burchardi, 2006), of low dose hydrocortisone (Annane et al., 2002; Sprung et al., 2008) and of intensive insulin (Brunkhorst et al., 2008; Van den Berghe et al., 2006).

COATS was calculated by multiplying the difference in costs per patient for a health service A compared to a health service B with the corresponding NNT. Multiplying the difference in costs per patient with the NNT, the cost per successful treatment results as COATS:

COATS = NNT x Δ costs (A - B) per patient.

If treatment A is put in addition to a standard treatment, the calculation of COATS is reduced to “NNT x costs per patient” for treatment A.

In the present study, the simplified “COATS = NNT x costs per patient” calculation was applied to assess COATS.

The range of costs that has to be expected regarding minimal and maximal estimated costs was expressed by the 95%CI of the NNT.

2.2 Data Analysis

NNTs with corresponding 95%CI and the resulting COATS are presented for different treatment regimens regarding morbidity and mortality.

3. RESULTS AND DISCUSSION

3.1 COATS and Significant Clinical Results

3.1.1 COATS and mortality

Due to the original study, application of rhAPC in addition to standard therapy in patients with severe sepsis with APACHE II ≥ 25 or multiple organ dysfunction syndrome (MODS) did cost € 7,400 per patient (Bernard et al., 2001; Moerer and Burchardi, 2006). The NNT to avoid one additional death within 28 days due to sepsis by rhAPC was 16.4 (95%CI 9.6 – 55.6) (Bernard et al., 2001) (Table 1). According to the above algorithm "COATS = NNT x costs per patient", the costs to avoid one additional sepsis related death would have been 16.4 x € 7,400 = € 121,360. Considering the 95%CI, the minimal costs would have been 9.6 x € 7,400 = € 71,040 and the maximal costs would have been 55.6 x € 7,400 = € 411,440.

Underlying meta-analyses with significant effects on mortality, such as low dose hydrocortisone in septic shock (Annane et al., 2009) or intensive insulin therapy in subgroups of patients with severe sepsis (Ellger et al., 2008) or of surgical critically ill patients (Griesdale et al., 2009), NNT and COATS can be calculated (Table 1).

3.1.2 COATS and morbidity

In a meta-analysis, morbidity, defined as critical illness polyneuropathy (CIPNP), was lowered by intensive insulin therapy in severe sepsis (Ellger et al., 2008). Thus, NNT (mean 10.2, 95%CI 6.8 - 20.7) and COATS to avoid CIPNP in one patient in addition with € 734 in mean (95%CI, € 490 - 1,490) are definable.

3.2 COATS and No Significant Clinical Results

Regarding rhAPC, there was no effect on mortality in a recently completed clinical trial, the PROWESS-SHOCK trial (FDA, 2011), and in a meta-analysis (Friedrich et al., 2006) (Table 1). Also, there was no effect on morbidity in the original paper (Bernard et al., 2001). Thus, NNT and COATS are infinite. Also, despite low costs per patient, in original studies with no effect on mortality and morbidity with low dose hydrocortisone (Annane et al., 2002; Sprung et al., 2008) and intensive insulin therapy (Brunkhorst et al., 2008; Van den Berghe et al., 2006) in patients with severe sepsis or septic shock, NNT and COATS are infinite.

3.3 Costs Related to Life Expectancy

In more classical medical economic analyses, costs per one additional survivor are calculated related to life expectancy. For example, if life expectancy is computed at ten years and the mean costs for rhAPC are € 121,360, the costs per saved year are €12,136, and if the utility is computed at 0.5, the cost per QALY is € 24,272 (Table 1).

Regarding rhAPC, the estimates of costs per life year and costs per QALY were pounds 4,931 (around 6,051 €) and pounds 8,228 (10,097 €) for patients with severe sepsis and multiple organ dysfunction (Green et al., 2006).

Table 1. Simplified incremental cost-effectiveness analysis to assess costs of additional treatment success (ICER = COATS, i. e., NNT x costs per patient) and mean costs regarding life expectancy for therapies in critically ill patients concerning mortality

Therapy	Study	Patients	Mortality	Cost per patient (€)	NNT			ICER = COATS			Mean costs with life expectancy	
						95%CI			95%CI		10	5
					Mean	Min.	Max.	Mean	Min.	Max.	Years	Years
rhAPC (1)	Original study	severe sepsis / septic shock	↓*	7400 (7)	16.4	9.6	55.6	121360	71040	411440	12136	24272
rhAPC (2)	Original study	septic shock	n. s.	7400(7)	n. d.	n. d.	∞	n. d.	n. d.	∞	n. d.	n. d.
rhAPC (3)	Meta-analysis	severe sepsis / septic shock	n. s.	7400(7)	n. d.	n. d.	∞	n. d.	n. d.	∞	n. d.	n. d.
Hydrocor-tisone (4)	Meta-analysis	severe sepsis / septic shock	↓*	39 (8)	15.4	8.3	98.8	601	324	3853	60	120
IIT (5)	Meta-analysis	severe sepsis >3 days ICU	↓*	72 (9)	13.2	6.9	143	950	497	10289	95	190
IIT (6)	Meta-analysis	Surgical ICU	↓*	72 (9)	22.7	14.3	56	1634	1030	4003	163	326

CI - confidence interval; COATS - costs of additional treatment success, i.e., NNT x costs per patient; ICU - intensive care unit; ICER - incremental cost-effectiveness ratio; IIT - intensive insulin therapy; NNT - number needed to treat; rhAPC - recombinant human activated protein C; n. s. - not significant; n. d. - not definable; ∞ - tends to infinity; ↓ - significantly reduced, i. e., $p < 0.05$; (1) = Bernard GR, 2001; (2) = FDA, 2011; (3) = Friedrich JO, 2006; (4) = Annane D, 2009; (5) = Ellger B, 2008; (6) = Griesdale DE, 2009; (7) = Moerer O, 2006; (8) = Annane D, 2002; (9) = Van den Berghe G, 2006.*

4. DISCUSSION

The present paper demonstrates that budget-related clinical decision making by ICER by practicing physicians may be facilitated by calculation based on data that is COATS, i. e., the product of the difference in treatment costs per patient and the NNT. Applying this simplified form of ICER, costs for reaching clinical endpoints, such as avoiding one additional death can be determined, if studies provide significant results with NNTs. The range of estimated costs at minimum and at maximum to reach distinct clinical endpoints can be expressed by the 95%CI of the NNT. On the other hand, it becomes obvious for physicians that they hardly can justify their therapeutic decisions, when the NNTs and COATS are tending to infinity regarding clinical endpoints, if therapies are not supported by significant results. Taken together, we suggest physicians should use a simplified from of ICER, that is COATS, to estimate the range of costs to reach distinct clinical endpoints due to studies with significant results or to reassess therapies without significant results in original papers or meta-analyses under the aspect of limited resources and budget-related decisions.

The calculation of COATS is in fact nothing else than an ICER. However, physicians are more used to deal with NNT than with ARR in scientific papers and in clinical decision making to reach specific aims and clinical endpoints. ICER to asses COATS based on data (NNT) in a transparent form is probably a more useful information for the physician at the bedside who has to decide based on her/his own evaluation than ICERs which may reflect in a much less transparent form an appraisal based on values, such as QALYs.

Cost-utility analysis (CUA) is a form of economic analysis used to guide procurement decisions. In health economics, the purpose of CUA is to estimate the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiaries. Hence it can be considered a special case of cost-effectiveness analysis. Cost is measured in monetary units. Benefit needs to be expressed in a way that allows health states that are considered less preferable to full health to be given quantitative values. In health technology assessments (HTAs) it is usually expressed in QALYs. The concept of QALYs was proposed by economists (Drummond et al., 1997). Despite of several known limitations (Porzsolt et al., 2010), this concept is - from an economic point of view - still one of the best to make allocation decisions in health care. In the calculation of QALYs, the quality of a fixed bundle of goods is rated by proxies and finally translated into a virtual product of quantity and self-rated quality of life. With the simplified form of ICER based on data (NNT) to assess COATS, we provide an easy to perform and transparent tool for budget-related decisions for physicians which is driven by clinical reasoning facilitating their acceptance and use.

In an ICER regarding rhAPC from the perspective of a third party payer, that is, the National Health Service (NHS) in England and Wales, costs associated with patient care from the NHS and the personal social services were included, together with all known patient benefits. The estimates of costs per life year and costs per QALY were pounds 4,931 (at around 6,051 €) and pounds 8,228 (at around 10,097 €) for rhAPC for patients with severe sepsis and multiple organ dysfunction (Green et al., 2006). In this analysis, a huge amount of variables was included, such as life expectancy data, baseline risk, effectiveness data, adjustment of life expectancy data, health state value, hospital resource use, cost data (such as for rhAPC, serious bleed, hospital costs per day in ICU and on other ward), long-term NHS costs, future costs and future benefits (life years). The authors concluded that whereas the therapeutic cost for rhAPC appears high (at around pounds 5,000 per patient) and the potential impact on the provider budget is considerable, rhAPC is clinically effective,

represents a cost-effective use of resources, and is a significant advance in the treatment of severe sepsis in patients requiring intensive care. However, most of these data are not available for physicians at the bedside, and calculations much to complex to perform for them, to take them into account for budget-related decisions to reach distinct clinical endpoints they are interested in, such as lowering mortality or morbidity.

Practicing physicians make clinical decisions based on original papers or meta-analyses, which may be included in guidelines they adhere to. In this context, COATS could be given for the aim of lowering mortality in the original paper regarding rhAPC, and in meta-analyses regarding hydrocortisone or IIT in distinct subgroups of patients (Table 1). On the other hand, COATS revealed that costs are tending to infinity, if therapies are not supported by significant results. This was the case regarding effects on mortality of hydrocortisone and IIT published in original articles and of rhAPC published in original articles and meta-analysis (Table 1), respectively.

COATS may lead to congruent or discordant estimations, underlying NNTs generated by original studies, meta-analyses or subgroup analyses regarding effects of treatment on distinct events and clinical endpoints (Table 1). F. e., the expected COATS regarding effects of IIT on mortality was not definable in all, mixed and medical patients, however explicable in surgical patients (Griesdale et al., 2009) (Table 1). Thus, COATS enables physicians to calculate in their setting of patients and decide on the basis of cost-efficiency for successful therapy.

We have to state that ICER based on NNT to assess COATS has limitations and does not reflect all costs attributable to a treatment in addition. COATS does not consider costs related to adverse effects and costs during the survival period. For example, despite low drug costs per patient with € 72 (Van den Berghe et al., 2006), in patients with severe sepsis, a reduction in mortality and morbidity, defined as mean score for organ failure, respectively, could not be demonstrated with intensive insulin therapy (Brunkhorst et al., 2008). Thus, NNT and the costs reflected by COATS are tending to infinity regarding mortality (Table 1) and morbidity. However, COATS does not point out the cost driving effect of this regimen due to the fact that the rate of severe hypoglycemia and of serious adverse events was significantly higher in the intensive-therapy group than in the conventional-therapy group (Brunkhorst et al., 2008). Therefore, due to the risk / benefit ratio and not due to the cost / benefit ratio, this study was stopped early for safety reasons.

We have to be very cautious with cost-effectiveness or efficacy analyses. With many drugs, results are very controversial with new studies not confirming positive results reported with the initial randomized controlled trial (RCT). This has been the case with original papers regarding rhAPC (Bernard et al., 2001), hydrocortisone (Annane et al., 2002) or IIT (van den Berghe et al., 2001) and subsequent original trials (Brunkhorst et al., 2008; FDA, 2011; Sprung et al., 2008) in distinct subgroups of patients. In detail, f. e., rhAPC in the initial RCT (Bernard et al., 2001) significantly reduced mortality, reporting a NNT to avoid one additional death of 16.4 (95%CI 9.6 – 55.6), resulting in COATS of € 121,360 (95%CI € 71,040 - € 411,440) (Table 1). However, underlying a meta-analysis (Friedrich et al., 2006) demonstrating no significant effect on mortality, NNT and COATS are infinite. Moreover, in a recently completed clinical trial, the PROWESS-SHOCK trial (FDA, 2011) (Table 1), rhAPC failed to show a survival benefit, resulting in a voluntary market withdrawal of rhAPC. Despite the market withdrawal of rhAPC, we chose this illustrative example of an expensive treatment recommendation to demonstrate the potential of COATS to help physicians in budget-related decisions in times of limited resources. These examples of original trials or

meta-analyses outline the absolute necessity to be very cautious when interpreting cost saving or cost-efficacy ratio, and to regularly reevaluate recommendations.

Resources of health care systems are limited. Rationing decisions by physicians differ from those of the government (Pearson, 2000). The health care economy must compete with other social priorities and thus, marginally beneficial care should be rationed for the overall public good (Pearson, 2000). However, rationalization is complex, and societies should try to apply therapies with the best cost-effectiveness by defining subgroups of patients who benefit best. This is illustrated by the calculation of the estimated costs at minimum and at maximum to reach distinct clinical endpoints in the example with rhAPC in Table 1. Proportional advocacy by physicians requires a critical weighing of risk and benefit in every clinical decision (Pearson, 2000). In this regard, NNTs and the 95% CI may help to define the subgroups of patients in the low range of NNT with the best risk / benefit and cost-efficiency ratio. Moreover, structuring clinical endpoints in a hierarchy, f. e. lowering mortality, avoidance or reversal of shock or adverse events, such as number and duration of organ dysfunction, morbidity or length of stay on the ICU or in hospital, COATS may help physicians to become aware of the costs associated to reach distinct endpoints. On the other hand, if trials are negative, NNT tends to infinity. Therefore, whatever the costs are, COATS regarding the defined endpoints is infinite.

5. CONCLUSION

ICER based on NNT to assess COATS, i.e., the product of treatment costs per patient and the NNT, is an easy to conduct and transparent tool based on clinical reasoning for budget-related decisions of physicians in times of limited financial resources. Applying COATS, costs for reaching distinct endpoints are predictable, if studies provide significant results with NNTs. Underlying the 95%CI of the NNTs, estimated costs at minimum and at maximum to reach distinct clinical endpoints can be given. Calculating COATS, it becomes obvious that costs are tending to infinity, if therapies are not supported by significant results. In contrast to the physicians caring for individual patients, for medical managers, other tools, such as QALYs, may be necessary to perform calculation of the costs for the community and the adequate allocation of health care resources, which better reflect complex weightings regarding variables such as effectiveness data, baseline risk, adjustment of life expectancy data, health state value, short-term and long-term costs, costs for different third party payers such as national health services, future costs and future benefits (life years) and cost-effectiveness acceptability.

CONSENT

In this paper, only published data from the literature were used for calculations and comparisons. Thus, a statement of patient consent is not applicable for this paper.

ETHICAL APPROVAL

Since data from the literature, only, were used for calculations and comparisons, ethical approval is not applicable to this paper. This study is not against the public interest. All authors hereby declare that all calculations and comparisons have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Annane, D., Bellissant, E., Bollaert, P.E., Briegel, J., Confalonieri, M., De Gaudio, R., Keh, D., Kupfer, Y., Oppert, M., Meduri, G.U. (2009). Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA, 301, 2362-2375.

Annane, D., Sebille, V., Charpentier, C., Bollaert, P.E., Francois, B., Korach, J.M., Capellier, G., Cohen, Y., Azoulay, E., Troche, G., Chaumet-Riffaud, P., Bellissant, E. (2002). Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA, 288, 862-871.

Bernard, G.R., Vincent, J.L., Laterre, P.F., LaRosa, S.P., Dhainaut, J.F., Lopez-Rodriguez, A., Steingrub, J.S., Garber, G.E., Helterbrand, J.D., Ely, E.W., Fisher, C.J., Jr. (2001). Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med, 344, 699-709.

Brunkhorst, F.M., Engel, C., Bloos, F., Meier-Hellmann, A., Ragaller, M., Weiler, N., Moerer, O., Gruendling, M., Oppert, M., Grond, S., Olthoff, D., Jaschinski, U., John, S., Rossaint, R., Welte, T., Schaefer, M., Kern, P., Kuhnt, E., Kiehntopf, M., Hartog, C., Natanson, C., Loeffler, M., Reinhart, K. (2008). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med, 358, 125-139.

Dellinger, R.P., Carlet, J.M., Masur, H., Gerlach, H., Calandra, T., Cohen, J., Gea-Banacloche, J., Keh, D., Marshall, J.C., Parker, M.M., Ramsay, G., Zimmerman, J.L., Vincent, J.L., Levy, M.M. (2004). Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med, 32, 858-873.

Dellinger, R.P., Levy, M.M., Carlet, J.M., Bion, J., Parker, M.M., Jaeschke, R., Reinhart, K., Angus, D.C., Brun-Buisson, C., Beale, R., Calandra, T., Dhainaut, J.F., Gerlach, H., Harvey, M., Marini, J.J., Marshall, J., Ranieri, M., Ramsay, G., Sevransky, J., Thompson, B.T., Townsend, S., Vender, J.S., Zimmerman, J.L., Vincent, J.L. (2008). Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med, 36, 296-327.

Drummond, M.F., Stoddart, G.L., Torrance, G.W. (1997). Methods for the economic evaluation of healthcare programmes. Oxford University Press, Oxford, New York.

Ellger, B., Westphal, M., Stubbe, H.D., Van den Heuvel, I., Van Aken, H., Van den Berghe, G. (2008). Glycemic control in sepsis and septic shock: friend or foe? Anaesthesist, 57, 43-48.

FDA. (2011). FDA Drug Safety Podcast for Healthcare Professionals: Voluntary market withdrawal of Xigris [drotrecoginalfa (activated)] due to failure to show a survival benefit. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm277212.htm, October 25.

Friedrich, J.O., Adhikari, N.K., Meade, M.O. (2006). Drotrecoginalfa (activated): does current evidence support treatment for any patients with severe sepsis? Crit Care, 10, 145.

Green, C., Dinnes, J., Takeda, A.L., Cuthbertson, B.H. (2006). Evaluation of the cost-effectiveness of drotrecoginalfa (activated) for the treatment of severe sepsis in the United Kingdom. Int J Technol Assess Health Care, 22, 90-100.

Griesdale, D.E., de Souza, R.J., van Dam, R.M., Heyland, D.K., Cook, D.J., Malhotra, A., Dhaliwal, R., Henderson, W.R., Chittock, D.R., Finfer, S., Talmor, D. (2009). Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ, 180, 821-827.

Moerer, O., Burchardi, H. (2006). The cost of sepsis. Anaesthesist, 55 Suppl, 1, 36-42.

Pearson, S.D. (2000). Caring and cost: the challenge for physician advocacy. Ann Intern Med, 133, 148-153.

Porzsolt, F., Pressel, H., Maute-Stephan, C., Kindervater, R., Geldmacher, J., Meierkord, S., Sigle, J.M., Eisemann, M. (2010). Appraisal of healthcare: from patient value to societal benefit. J Publ Health, 18, 297-302.

Sprung, C.L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., Weiss, Y.G., Benbenishty, J., Kalenka, A., Forst, H., Laterre, P.F., Reinhart, K., Cuthbertson, B.H., Payen, D., Briegel, J. (2008). Hydrocortisone therapy for patients with septic shock. N Engl J Med, 358, 111-124.

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P., Bouillon, R. (2001).Intensive insulin therapy in the critically ill patients. N Engl J Med, 345, 1359-1367.

Van den Berghe, G., Wouters, P.J., Kesteloot, K., Hilleman, D.E. (2006). Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med, 34, 612-616.

Worster, A., Rowe, B.H. (2001). Measures of association: an overview with examples from Canadian emergency medicine research. CJEM, 3, 219-223.