Step (or leap) into the future. What is new in 2000 and beyond? An emphasis on endocrine failure

A.E. Baue

This paper is my annual oration on prevention of multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF) at the Organ Failure Academy in Trieste, Italy. All we can do to treat MODS and MOF is organ support. Therefore, prevention is the key - supporting organ and system function before dysfunction or failure occur. There are many ways we can do that in 2002. I have reviewed them [1, 2]. The future was predicted recently by a number of authorities in intensive care medicine and anaesthesiology who were plenary speakers at the recent Society of Critical Care Medicine meeting. Buchman talked about the new junction of genomics and critical care as it exists today and as it is likely to evolve tomorrow. van der Pol reviewed tissue factor and activated protein C, which may also improve other inflammatory pathways. Abraham reviewed genetic analyses and predicted that they may help determine future therapies in critically ill patients. Tracy said that it should be feasible to study both vagus nerve stimulation and anti-HMGB-1 (a latent mediator). Vincent reviewed future therapeutic interventions that will likely involve multiple/combination therapies. Genomics and critical care, tissue factor and activated protein C, genetic analysis, latent mediators, and other problems, and the possibility of multiple or combination therapy are on the horizon. This last recommendation comes because factors to either block or stimulate individual mediators or anti-inflammatory agents have failed. The real question is how quickly these predictions will help our patients. The world of science and molecular biology is exciting but much of it is pure science and is not yet related to improved care in the intensive care unit (ICU) or operating room.

Complex diseases and clinical scientific studies – outcomes research, evidence-based medicine

Rees [3] wrote about the importance of clinical research – clinicians describing

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diseases and trying various approaches, medications, and therapy. Rees is a dermatologist and cites three important examples from dermatology. First, acne improved in some patients that took retinoids. This was an accidental observation and then was tried clinically. Now the standard treatment of acne is with retinoids. Secondly, observations of seborrheic dermatitis suggested involvement of yeast. Anti-fungal drugs were tried and are now the treatment of choice for this abnormality. Psoriasis seemed better in patients who were out in the sunshine. Ultraviolet lamps were developed for this abnormality with excellent results. All three problems had therapy developed from clinical observation and not from basic science or molecular biology. Rees states, "Despite the mushrooming of basic research, clinical breakthroughs have become less common. It is this gap (between medicine and biology) that needs to be closed but unlike many, I don't believe it will be resolved by clinicians learning more genetics; rather it is geneticists and biochemists who need to learn some medicine." Simon [4] put it well saying, "Medical schools have become schools of molecular biology and biochemistry rather than schools of medicine."

Clinical research may be translational research, translating basic discoveries into clinical therapy. This may involve clinical trials, behavioural research, epidemiology, outcomes research or observation of patients. Nathan [5] writes about careers in translational clinical research – historical perspectives, future challenges, the importance of clinicians trying to assimilate basic discoveries and information on patient care.

There is now a big push for "outcomes research" [6]. As a clinician, ask – What else is there for clinicians but outcome? Do our patients get better and survive? Anything short of outcome research is pure science, not patient care. The only determinant of clinical research is outcome.

There is now emphasis on "evidence-based medicine" [7]. I ask – What is the alternative –lack of evidence medicine - or no evidence medicine? Evidence -based medicine is what we all do. How do clinicians do anything other than therapy based upon evidence? The evidence may be our own observations, which is fine. There may never be large randomized trials. Not everything will ever be subjected to randomized trials, which evidence-based medicine professionals may believe are necessary.

The three pillars of evidence based medicine are: (1) are the results valid? (2) what are the results? (3) how do I apply the results to the care of my patients?

A controlled trial is the best way to decide whether an agent helps or not. Is that the only way to go or can we have a collection of anecdotes of a satisfactory response? An example is the agent botox. If a woman has wrinkles, botox is injected and the wrinkles go away. Is that not evidence-based medicine, without a controlled trial? How would you carry out a controlled trial for perforated

diverticulitis? What about squamous cell carcinoma? How would you do a controlled trial? No treatment, late treatment, whatever? The same thing with an acoustic neuroma. What would be the controls? How do you perform a controlled trial in such cases?

Observation of patients by clinicians in the ICU is still critically important. We must observe our patients. We must recognize outcome. Who does poorly and why? Who recovers and why do they recover? What are the characteristics? Can we dissect this? What are the trends in deterioration or recovery? What are the disasters? What are similarities and differences in various disease processes? Are there any surprises that we should learn about? Observation of patients in ICU by good doctors is critically important as we try to improve care.

What is new in 2002? What have we given up now? What have we recognized now?

It is now generally accepted that attacking single elevated or decreased mediators will not work [8]. Many magic bullets have failed. No single agent, to give or block, is helpful in all patients with sepsis or infection. It has taken a long time for the idea that there are no single magic bullets to be accepted. We have also given up trying to treat patients in pro- or anti-inflammatory phases. Pro-inflammatory agents and mediators begin the process and are quickly followed by anti-inflammatory agents. It is not possible to describe what phase a patient is in because they are always in both phases until they recover. This has prevented a lot of nervous indigestion. A senior member of the Shock Society once said, "If only we knew where a patient was in the pro- anti-inflammatory response, then therapy would be easy". This is no longer true.

Marshall et al. [9] described the putative or prognostic markers of sepsis and divided them into the categories listed in Table 1. They listed 80 such putative markers associated with a poor outcome, however, none help in treatment.

With sepsis, severe sepsis, septic shock, and lethal sepsis, what is the

Table 1 Putative (prognostic) markers of sepsis

Microbial products	Cytokines
Physiological parameters	Acute-phase reactants
Haematopoietic cells	Cellular processes
Cell surface markers	Miscellaneous
Mediators of coagulation	Soluble receptors

disease? We must break down and define the disease rather than the general concept of sepsis. We cannot treat sepsis. Inflammation is necessary with injury and infection. Can we ever hope to control excess inflammation without harming the patient?

Can we ever understand, assimilate, and develop a coherent scheme of the complexities of injury, infection, markers, mediators, inflammation, and genetic polymorphisms? Marshall et al. [9] developed a new classification similar to a cancer classification of local cancer, metastatic spread, and spread to lymph nodes in which I is for infection, R response, and O organ dysfunction – IRO. Another classification is PIRO, in which P is for predisposing factors [10]. These are classified on a scale of mild, moderate, or severe.

We now recognize that a marker indicating that death of a patient is likely, does not help us treat the patient. Prediction is interesting but of no therapeutic value. Recognition that scoring classification systems correlate with prognosis has not helped us with therapy. The concept of excessive inflammation is scientifically interesting but has not helped treatment.

Autoimmune inflammatory disease is now recognized as more than just inflammation. Mediators are involved that are quite specific for each of the diseases. Many are treatable by blocking or additive agents for these mediators. The difference in treating such diseases and the treatment of sepsis in general is that these are specific diseases in which the abnormalities have been well outlined and are quite specific. They are not the generalized aspects of infection or of sepsis. For example, with systemic lupus erythematosus, tumor necrosis factor (TNF-α) is under-expressed, as are trasforming growth factor (TGF)b and TGFbr in T cells. In addition, interferon-γ is over-expressed in the skin. In rheumatoid arthritis there is under-expression of interlukin (IL)-1ra and over-expression of TNF-α. Inflammatory bowel disease is more complex with TNF-α over-expression as are IL-2, IL-7, IL-10, IL-2r, IL-10r, and stat-4, and under-expression of stat-3 and TGFb [11, 12].

IV immunoglobulin helps idiopathic thrombocytopoenic purpura, Guillain-Barrè syndrome, myasthenia gravis, Kawasaki's disease, multiple sclerosis, and others [13]. Rheumatoid arthritis can be treated with TNFr: Fcp80 fusion protein, a human soluble TNF receptor (Immunex), IDEC-CD9.1 - an anti-CD4 monoclonal antibody, and recombinant human IL-1ra (Amgen) [14]. These agents depress the inflammatory process. Phase II trials are encouraging. Whether they will prevent later joint destruction is not known. Other inflammatory diseases helped by specific anti-inflammatory agents are shown in Table 2.

Table 2 Inflammatory disease helped by anti-inflammatory agents

Rheumatoid arthritis	Anti-TNF mAb [14]
Crohn's disease	Alestron hydrochloride [15,16]
Ulcerative colitis	Lotronex – this helped many. There were a few deaths
	Now growth hormone is also believed to be effective
Chronic granulomatous disease	IFN-γ decreased infections [17]
Ankylosing spondylitis	Anti-TNFab – Etanercept – (arhTNFr) (P75): Fc fusion protein [18,19]

New harbingers of doom

Many measurements predict disaster in our patients - changes in the immune response, changes in mediators, and others. So far, they do not help us in therapy. I question whether they ever will. Recent predictors of disaster include absolute monocyte and CD13 LADR ROC counts [20]. An early lower depression and later improvement of HLA-DR and lipopolysaccharide (LPS) stimulated IL-6/TNF-α occurs in survivors of sepsis [21]. There is a lower basal plasma cortisol and response to corticotrophin releasing hormone (CRH) in non-survivors - an example of endocrinological organ dysfunction that I review later [22]. Over-expression of high-affinity Fcr receptor (CD64) is associated with leukocyte dysfunction in sepsis and ultimate mortality [23, 24]. Splenic gene expression shows differences in severe sepsis/MODS [25]. IL-6 levels are higher in non-survivors [26]. The number of blood transfusions correlates with increased mortality [27]. The TNF-α/TNFR ratio correlates with MODS score and mortality. Protease activation in the gut is an early indicator of MOF [28]. Nitrite/nitrate and type II phospholipase A_2 increase with MODS and mortality [29]. Impaired monocyte IL-12 production predicts a lethal outcome in sepsis [30]. IL-18 appearance predicts an adverse outcome with sepsis [31]. Type III protein secretion predicts a poor outcome [32]. There is a higher order of activation of NK-kB in non-survivors compared with survivors [33]. Fibrinolysis is activated and ATIII utilized more in severe septic shock [34]. Peaks of granulocyte colony-stimulating factor (G-CSF) and polymorphonuclear neutrophil leukocyte (PMN) burst activity predict septic shock [34]. Serum IL-1 and monocyte IL-1 are increased in fatal sepsis. A blunted rise in platelet count predicts a worse outcome [37]. Fas (CD95) ligand is increased on mononuclear cells and indicates decreased survival [38]. Heat shock protein 70 (HSP 70) protects in sepsis [39]. There is apoptosis of bronchoalveolar lavage cells in patients who eventually die of sepsis [40]. Low pre-operative endocab levels predict a poor outcome. Human toll-like receptor mutations are associated with

increased mortality [41]. Serial lactate levels predict MOF [42]. α-Atrial natriuretic peptide, cyclic guanosine monophosphate, and endothelin in plasma are markers for mortality [43]. Decreased procalcitronin and C-reactive protein were associated with survival [44]. Platelet and leukocyte activation correlate with severity of sepsis [45]. Failure of neutrophil chemotactic function contributes to sepsis outcome [46], as do other PMN functions [47].

Xigris – Where does it stand?

Xigris is drotrecogin alfa activated (Lilly) or recombinant human activated protein C (rhAPC). This seemed like a miracle drug when the PROWESS trial reported on efficacy and safety of rhAPC for severe sepsis [48]. This multicountry double-blind, placebo-controlled trial with 1,690 patients had mortality with placebo of 30.8% and with APC of 24.7%. This is a risk reduction of 6.1%, not a great difference, even though it is statistically significant. It is necessary to treat 16.4 patients to save 1 patient. It costs about U.S. $22,100 per case and roughly U.S. $7,000 a dose. It requires a very careful protocol, excluding all patients who have bleeding, coagulation disorders, or a high risk of bleeding. It may contribute to bleeding. In this trial there was decreased production of TNF by monocytes, decreased interaction between neutrophils and endothelial cells, less tissue ischaemia, and less E-selection production. Plasma D-dimer levels indicated decreased pro-coagulant activity, with decreased serum IL-6 and inflammatory mediators. Thus, it may be an anti-inflammatory agent, as well as correcting coagulation abnormalities [49]. An absolute reduction in risk of death of 6% is not huge, but it is an important first step. Use of the drug must be carefully monitored because it could raise the risk of bleeding. Another problem is that the PROWESS trial was paid for by the Eli Lilly Company who manufactures the drug. The director of the study, Bernard, is a Lilly consultant. Seven of ten other authors are Lily employees, stockholders, or consultants. Could this have influenced the outcome?

The recent MARGAUX Conference (November 2001) on "The endothelium – an unrecognised organ in critical illness" – was sponsored by the Eli Lilly Company, which makes Xigris. Much of the conference had to do with the effectiveness of rhAPC. Publication as a supplement to Critical Care Medicine was paid for by Lilly [50]. Of the 25 participants, all received an honorarium. Seven were consultants to Lilly, 2 were employees, 1 was on their Speaker's Bureau, 2 were Lilly investigators, and 2 were Lilly researchers. One was both a researcher and an investigator. Could these relationships have influenced the study?

Endotoxin

Endotoxin has been studied extensively for many years. There is no doubt that it is present in the walls of gram-negative bacteria and when injected causes difficulty. How does all this knowledge help us to better care for our patients? Monoclonal antibodies to endotoxin do not help. Blocking endotoxin does not help. It is not possible to treat the presence of endotoxin. All of this interesting information about gram-negative bacteria, infection and endotoxin has not led, as far as I know, to a single positive effect in the treatment of patients.

Mutations and polymorphisms are a hot topic

Much research has been carried out to determine polymorphisms or mutations that may increase the risk of infection and death or occur in certain clinical circumstances. Some of these are shown in Table 3. Many predict that studies of these mutations and polymorphisms will be a big help in taking care of patients when they can be measured early in an illness, with prediction as to what might happen. However, there are major differences in studies. Some found that CD14 increases in sepsis, others that it did not [55]; the same was found with TNF polymorphism. Randolph [55] points out that "bias population stratification, high variability in the sepsis phenotype (and small studies) could explain the discrepant findings". Cariou et al. [56] predicted that future technology will "revolutionize medicine" such as gene chip array will help determine patient susceptibility, prognostic risk factors, quicker diagnosis, and the accurate prediction of response to drugs. However, Willett [57] pointed out that

Table 3 Mutations and polymorphisms related to clinical circumstances

Human-toll like receptor – r(hTLR4) mutations – increased risk of gram-negative infection and death [41]
IL-6 polymorphism – decreased IL-6 in appendicitis
TNF genetic polymorphisms – no influence on outcome of sepsis [51]
The C-159T CD14 promotor – genetic polymorphism affects susceptibility to shock and death [52]
No association between CD14 (C-159T) polymorphism and sepsis
Allele IL-1 associated with susceptibility to sepsis [53]
IL-1 receptor antagonist gene – increased sepsis [54]
TNF-alpha promotor polymorphism – increased sepsis
LPS binding protein gene – increased sepsis
Plasminogen activating factor-1 gene – increased sepsis.

overly enthusiastic expectations regarding the benefits of genetic research for disease prevention may upset research priorities and spending for health. Integration of genetic information into epidemiological studies can clarify causal relations between lifestyle, genetic factors, and risks of disease. A potential contribution of genomic research to disease prevention is in malignancy such as breast cancer, low density lipoprotein receptors for cholesterol and other areas where diseases may be prevented. Strohman [58] issued a warning, "Cell and molecular biology, in conjunction with new theoretical developments, have, in the past decade, taken us from a grossly naïve view of genetic determination (that complex traits are caused by a single gene) to the stark reality that almost all human diseases are complex, context dependent entities to which our genes make a necessary but only partial contribution." The new genetics will not revolutionize the way in which common diseases are identified or prevented. This stems from incomplete penetrants of genotypes for common diseases, limited ability to tailor treatment to genotypes and low magnitude of risk conferred by various genotypes. Roos and Winterbourn [59] noted that differences in social structure, lifestyle, and environment account for much more disease than do genetic differences. Epistasis is defined as a single genetic locus that may have only a small effect and may depend on other genetic loci and their relationships.

Endocrine system failure joins the list of organ system failures

Not only can the circulation, lungs, liver, kidneys, gut, musculoskeletal system, nervous system, and the metabolism-nutrition system fail, but now we recognize that the endocrine system can also fail. Back in the early 1980s we performed a study in Munich, Germany, of patients in the surgical ICU who had severe life threatening illnesses. Some had septic complications, others had multiple system injuries [60]. Initially all such patients had a low T_4, low T_3, and a normal thyroid-stimulating hormone (TSH), which has been called the low T_3 syndrome. Its significance is not known. At the same time, these patients had normal adrenocortico-tropic hormone, cortisol, prolactin, and growth hormone, but catecholamines and insulin levels were high. In survivors the T_4 and T_3 levels increased to normal and catecholamines returned to normal. In patients that died, there were further decreases in T_4, T_3 and TSH and a great increase in epinephrine. There was no change in TSH when these patients received protirelin (TRH). We concluded that there was hypothalamic-pituitary dysregulation or suppression with altered release or metabolism of T_4 and a question of thyroid insufficiency. The high concentrations of catecholamines mediate

the hypermetabolic response to injury and infection. There was a reciprocal relationship between thyroid hormone levels and catecholamine levels in some patients. We also recognized that some patients with severe and prolonged stress had cortisol levels that were lower than would be predicted. Thus, the hypothalamic-pituitary dysregulation or suppression was related to the severity of injury and potential death of these patients. We raised the question as to whether this represented hormonal insufficiency for cell and organ function, which is detrimental to the individual or inability to synthesize neuropeptides and other hormones, or the downregulation of a dying organism. This remains to be determined. Sibbald et al. [61] also recognized some years ago that there were variations in adreno-cortical responsiveness during severe bacterial infection. They suspected unrecognized adreno-cortical insufficiency in patients with severe bacterial infection.

There have been recent reports of dramatic effects of corticosteroids. van Leeuwen et al. [62] found a superphysiological dose of corticosteroids in late septic shock to reverse a downhill course in an elderly woman. They thought that this was directly related to inhibition of nuclear factor-kB in peripheral blood mononuclear cells. Annane [63] reported that a dose of hydrocortisone every 6 h intravenously and a dose by mouth of fludro cortisone reduced mortality by 30% in septic shock patients who were non-responders to ACTH. Beishuizen et al. [64] found extremely low corticosteroid binding globulin (CBG) levels in early septic shock and multi-trauma. They believe that CBG plays an active role in glucocorticoid response in severe stress and regulation of cortisol. Schroeder et al. [22] found an altered response to corticotropin--releasing hormone (CRH) in patients with severe sepsis. Their patients had a decreased basal plasma cortisol level, and an impaired response to a single CRH dose in non-survivors, which they called endocrinological organ dysfunction. Kees et al. [65] found a high incidence of adreno-cortical insufficiency in patients with MODS. They recommended assessing adrenal function in all critically ill patients.

Zaloga [66] reported that pharmacological short-dose therapy with glucocorticoids did not improve outcome in patients with sepsis and septic shock. However, treatment of these patients with longer courses of stress-dose glucocorticoids, such as 100 mg of hydrocortisone every 8 h for 1-2 weeks, may be effective. Two recent prospective randomized, placebo controlled clinical trials of stress-dose hydrocortisone therapy have demonstrated beneficial effects on outcome in patients with septic shock [67, 68].

Namba et al. [67] reported that methylprednisolone suppresses not only the inflammatory cytokines but also anti-inflammatory cytokines in patients with septic shock. Whether or not this helps patients is unclear. Other hormonal

changes that occur with stress are increased levels of epinephrine and norepinephrine. Generally there is increased serum cortisol levels and ACTH. There is blunted growth hormone pulsatility, the so-called SICU thyroid syndrome described earlier, an acute decrease of dehydroepiandrosterone and testosterone levels, with increased prolactin and insulin resistance. Ligtenberg et al. [69] also believe that there is relative adrenal insufficiency, and the best available clue to its diagnosis is rapid clinical and haemodynamic improvement of catecholamine-dependent patients after substitution with 300 mg or less of hydrocortisone per day. This is the low-dose corticosteroid therapy for 1-2 weeks. Thus, relative adrenal insufficiency seems treatable, with promising preliminary results with hormone releasing factors.

Further evidence for endocrine failure is that in septic shock there may be inappropriately low levels of vasopressin, partly related to a depletion of vasopressin stores in the neurohypophysis [70].

Meduri et al. [71] found that giving steroids intravenously for 1-2 weeks at doses of only a fraction of those used in the 1980s megadose studies allows patients to be weaned from a ventilator, and acute respiratory distress syndrome (ARDS) can be helped significantly. The Meduri studies have all been small, sometimes anecdotal, with no large trials. A reason for this is that the steroids are very inexpensive and are not going to benefit the drug companies very much. The new drug Xigris is much more exciting and will be a much bigger earner for the Eli Lilly Company.

Another recent development is the study and use of perioperative stress-dose steroids, raising the question as to whether they make a difference. Nagelschmidt and Neugebauer [72] found improvement of outcome after abdominal surgery by preoperative high-dose methylprednisolone. The benefits of this therapy were more pronounced in patients having major operations. Brown and Buie [73] reviewed this recently: "Our systematic review of the literature provides convincing evidence that 'stress' steroids are unnecessary. Maintaining patients on their preoperative glucocorticoid dose does effectively prevent hypotensive crises and may avoid the potential complications of higher dose steroids."

Koo et al. [74], in an animal model of sepsis, found that adrenal insufficiency occurred with reduction in corticotropin-induced plasma corticosterone release and adrenal content of small AMP, as well as decreased adrenal levels of corticosterone.

The argument goes on as to whether corticosteroids should be given in all patients with septic shock. There is a downside, of course, with the possibility of infection. Not everyone is going to be able to study adreno-cortical function. My recommendation is that if all else fails, give corticosteroids a shot. The

patient could well have relative adrenal insufficiency and respond dramatically. High-dose methylprednisolone and high-dose glucocorticoid therapy in patients with systemic infection or severe sepsis and septic shock did not work and these have been reported previously in the literature from the Veterans Administration Study and the study by Bone et al. These are described well by Woolf in *Critical Care Medicine* [75] and by Matot and Sprung [76]. Briegel [77] described a reduction of vasopressors in septic shock when hydrocortisone was given. This works better if there is impaired adrenal function [78]. There are trends in better organ function with hydrocortisone and decreased mortality. This suggests a restoration of vascular reactivity of norepinephrine.

We keep hearing about non-linear systems and chaos theory – when will it help us?

The new concept in biology of integrative or non-linear biology and the application of chaos theory has been predicted to have a great impact on how we take care of patients and how we approach an inflammatory response. So far, it has not helped us. Schultz [79], in the Claude Bernard lecture to the American Physiological Society titled *Homeostasis, Humpty Dumpty and Integrated Biology*, described integrative biology. He stated, "In biology the parts are dynamic or plastic. They can change shape when they are brought together – that's what non-linearity means. The shape of the whole cannot be predicted by knowing only the shapes of the separated parts." If we substitute function for shape, we can see that the function of the whole cannot be predicted by knowing only the functions of the separate parts. This seems to be where we are now in trying to determine pro-inflammatory mediators, anti-inflammatory mediators, and whatever. Schultz goes on to say that molecular biology provides parts of a puzzle – "putting them together is the problem". He reviewed Cannon's homeostasis concept and believed that homeodynamics would have been a jazzier and technically more-correct expression. Buchman stated, "If nested non-linear models are better represented for human physiology than Cannon's collection of negative feedback servomechanisms, then therapy should be redirected towards transitions to a basal range – not therapeutically manipulating such things as cytokines or nitric oxide [80]. This is the concept that Siegel introduced many years ago in describing physiological and metabolic correlations with various human abnormalities [81].

Focusing on the phases of inflammation – pro, anti, etc. – would be Walter Cannon's approach. Blocking one mediator may change not only the effects of that mediator, but other mediators and the entire system. As Buchman also said,

"We are prolonging lives far beyond the limit and capacity of intrinsic physiological responses" [81]. Chambers and Buchman [82] compared Cannon with Lawrence J. Henderson. Henderson described systems as "a necessary postulate of biology is that no function of an organ is independent of another". Goodwin [83] said that the great gift of chaos theory is that traditional science cannot predict complex systems. Latour [84] said, "Science does not enter a chaotic society to put order into it any more --- but to add new, uncertain ingredients --- to the collective process." A major finding using this approach is that heart rate variability is normal. If heart rate becomes regular it is a sign of disease. Goldberger et al. [85] said recently that chaos in bodily functioning signals health, whereas periodic or regular behaviour foreshadows disease. This approach to human disease is potentially very exciting, but so far there is little that we can learn from it. It is all promise with little substance. There is nothing that I am aware of that we can use to better treat our patients. Thus, chaos theory will be important in the future, but there is no prediction when it will help us in patient care [86].

Multiple therapeutic agents for sepsis – what is sepsis?

Some have recommended multiple therapeutic agents for sepsis

There are many human diseases in which multiple agents are required for therapy, including anti-tuberculous therapy, immunosuppression for transplanted organs, inotropes and diuretics for heart failure, multiple antibiotics for polymicrobial peritonitis, cancer chemotherapy, and support of the gastrointestinal tract. Several tried therapy for excess inflammation, such as Knox et al. [87] using a combined chemotherapeutic regime in burn patients with antioxidants, vitamin C, E, and glutamine, an endotoxin binder (parenteral polymixin B), a cyclo- and lipoxygenase inhibitor, ibuprofen, and reconstituted human growth hormone. They believe this improved mortality, but their initial study was based on historical controls. Kirton et al. [88] used a multi-agent approach for patients after trauma – a three arm strategy to (1) block free radical production; (2) provide scavengers; (3) bolster natural defenses and normalize pHi. They then used a maintenance infusion for 24 h of hydrocortisone, selenium, lidocaine, polymixin B, vitamin C, and mannitol. It is difficult to show that combinations of agents are effective, and particularly the important agents in the cocktail.

The search for magic bullets continues, even though it is recognized that no single factor is likely to improve mortality all by itself. Some of the magic bullets

that have failed recently include nitric oxide synthase inhibitor (*N*g-methyl-L--arginine HCI). Diaspirin cross-linked haemoglobin increased mortality. *N*-Acetyl cysteine failed to improve mortality for sepsis, but it is important that it helps paracetamol (acetaminophen)-induced fulminant hepatic failure. Leptin in studies of obesity has not had much promise. Anti-thrombin III failed to improve mortality. P55TNF receptor fusion protein has not helped clinically, nor has TFPI (tissue factor pathway inhibitor). Recombinant human growth hormone increased mortality in all ICU patients, however it is very helpful in burn patients. LNAME increased mortality. So much for magic bullets.[89] Cohen [8] wrote recently, "Perhaps clinical trials in sepsis have not really 'failed' but rather have refuted the hypothesis that sepsis, as we define it at present, is a concept precise enough to be subjected to a clinical trial of a single therapeutic intervention". He also said, "First we must seek to break sepsis down into smaller, more homogeneous populations. (I have been preaching this for years.) Secondly, we might develop 'packages of care', combining several types of interventions simultaneously. There are many problems with this realistic approach." [8]

Prevention

Prevention of MODS and MOF, prevention of nosocomial infection, prevention of ventilator pneumonia, and prevention of antibiotic resistance all require attention in order to safeguard our patients in the ICU, prevent complications and further deterioration.

The principle is to support organ function, to prevent dysfunction/failure. It is necessary to recognize early dysfunction and increase supportive efforts wherever possible. We must also strive to prevent complications such as further infection, spread of infection, nosocomial infection with resistant organisms, ventilator-associated pneumonia, thrombophlebitis, stress ulcer bleeding (best prevented by omeprazole), and catheter-associated problems. Support of organ function and prevention of organ failure has been well described elsewhere, and there will be many references to it in the presentations in Trieste in November 2002. I provide references for excellent discussions and recommendations in this area [89, 90]. It is well recognized that nosocomial infection in ICUs is increasing. There is a continuing need to prevent ICU contamination, to keep the unit clean, to decrease likelihood of transmission from one patient to another and the development of resistant strains of organisms [89, 90].

The communicable disease centre in the United States has developed the National Nosocomial Infection Surveillance System (NNIS). They define and recognize infection control practitioners (ICP) and surgical auditors (SA) [91].

They have a division of microbiology and infectious diseases (NMID) that is studying anti-microbial resistance. There is a Needle Stick Safety and Prevention Act 2001 to try to eliminate blood-borne pathogens and a group called OPIM (other potentially infectious materials). A number of similar organizations have developed in Europe - KISS (Kraunkenhaus – Infection – Surveillance System), EPIC (European Prevalance of Infection in Intensive Care), HELICS group, and an NINNS team in England. In Italy there is the GISIS group (Gruppo Italiano di studio sulle infezion-gravi). There is also the Euro/NIS study group. Candiani [91] writing in *Minerva Anestesiologica* says, "Hospital leaderships and heads of most critical departments must – with great urgency – organize an educational program for the nursing and medical team working in critical areas".

Infection, on a surgical service, can occur in the lung, at the surgical site – (now called surgical site infections – no longer called wound infections), in the urinary tract, bloodstream, abdomen, catheters, skin and soft tissues, the colon and in other areas. Prevention of nosocomial infection in the ICU requires strict contact isolation, antiseptic technique, handwashing, vigorous environmental decontamination and anti-microbials used appropriately and adequately. Barie [92] says that infection control is a matter of self control - "We must wash our hands. We must use barrier precautions for catheter insertion. We must remove devices as soon as possible, use antibiotics judiciously for prophylaxis and therapy and – Wash our hands."

The whole thrust of Ignac Semelweis' great study and revolution was that puerperal sepsis could be eliminated by careful handwashing before delivery of a woman in labour [90]. What would Semelweis recommend today? He would recommend washing our hands before going from patient to patient in an ICU.

Infection in high-risk patients is of great concern. Early fluconazole use is of no help [93]. Selective decontamination of the digestive tract is of modest benefit [94]. Antibiotic-coated devices provide some help, but may also lead to resistance. There are now mucosa barrier support strategies and vaccines such as a *Staphylococcus* vaccine, which reduce the infection risk, particularly in renal dialysis patients [95]. Resistance of microorganisms to antibiotics continues to increase. The list gets longer (Table 4). There are now resistant pneumococci, *Klebsiella*, *Pseudomonas*, *Escherichia coli*, and *Proteus*, (also, malaria, tuberculosis, gonorrhea, and salmonella). Avoparein (vancomycin) is still used in cattle feed in Europe. Now Group A streptococcus has become resistant in some situations to erythromycin.

The Communicable Disease Center has a campaign to target anti-microbial resistance in hospitals, and they recommend 12 steps to prevent anti-microbial resistance among hospitalized adults (Table 5).

Table 4 Antibiotic resistance

Vancomycin Resistant *Enterococci* (nosocomial – VRE)	
Methicillin-resistant *Staphylococcus aureus* infection (MRSA)	
Resistant –	*Pneumococcus* *Klebsiella* *Pseudomonas* *Escherichia Coli* *Proteus* *Enterobacter*
Also resistant -	Malaria Tuberculosis Gonorrhea Salmonella
Group A streptococcus – some are resistant to erythromycin	
Tolerant fungi to Fluconazole	

Table 5 Twelve steps to prevent anti-microbial resistance among hospitalized adults

A.	Prevent infection.
1.	vaccinate
2.	remove catheters
B.	Diagnose and treat infection effectively
3.	target the pathogen
4.	access the expert
C.	Use anti-microbials wisely
5.	practice anti-microbial control
6.	use local data
7.	treat infection, not contamination
8.	treat infection, not colonization
9.	know when to say "no" to Vanco
10.	stop treatment when infection is cured or unlikely
D.	Prevent transmission
11.	isolate the pathogen
12.	break the chain of contagion.

There are some new antibiotic contenders, including Synercid, Zyvox, Harp-hetero aeromatic polycyclic compounds, and potentially agents that block PDF (peptide deformulate). There are also now many chronic diseases that are known to be of infectious origin, including *Helicobacter pylori*, which causes peptic ulcer and gastric cancer, *Borrelia burgdorferi* causing one form of arthritis and also brain disorders, *Chlamydia pneumoniae* causing acute respiratory infections and contributing to atherosclerosis, the human papilloma virus involved in cervical cancer, and hepatitis B and C in liver cancer.

A number of new microbicidal weapons are involved in neutrophil killing of infectious organisms. Both oxidative and non-oxidative mechanisms cooperate. In phagosomes, oxidative killing occurs with NADPH oxidase converting oxygen radicals to hydrogen peroxide, with myeloperoxidase there is HOCl and oxidative killing. There may also be hydroxyl radicals. In non-oxidative killing, granule proteases and elastases (cathepsin G) all bind to a proteoglycan matrix in azurophil granules. pH increases to 8. There is potassium ion influx and bacteria are killed.

There is now much more information available about problems with neutrophils in infection and in ICUs, particularly. There is a natural inhibitor of neutrophils – CC16 – that decreases neutrophil-mediated lung damage in ARDS [96]. There is now evidence that impaired neutrophil function precedes nosocomial infection. Neutrophil elastase may contribute to acute lung injury and inhibitors of elastase may help [97]. Suppressed neutrophil chemotactic responses with increased nitrate occur, particularly in non-survivors. Also, impaired neutrophil migration occurs with infection and nitric oxide from neutrophils is known to be a double-edged sword, helping in some circumstances and being harmful in others [98]. How do we separate them?

Thus, we must emphasize prevention. We must consider the problems of bacteria and antibiotic resistance and the ICU dilemma of cross contamination. One of the most-difficult things to enforce in an ICU is handwashing before going from one patient to another. Thus, the original message of Semmelweiss in Vienna many years ago is – wash your hands [90].

Contamination in ICUs can occur in a number of ways. Recently van Grafhorst et al. [99] found that *Staphylococcus* species were contaminating standard preparations of syringes for intravenous drug administration.

Koss et al. [100] found that, in caring for patients on a ventilator, protective contact isolation with gowns, gloves, and handwashing was not superior to gloves and handwashing alone in the prevention of airway contamination and nosocomial pneumonia in surgical ICU patients. This is not true for device insertion and other procedures when gowns, masks, gloves, and handwashing are necessary.

Therapy which may help certain patients in the ICU

There are a number of individual therapies, each of which provide some improvement in sick patients in an ICU, but may not by themselves change mortality. These include pentoxifylline [101, 102], AT3 in septic patients, [103, 104], enteral immunonutrition [105], iDo2 and VO2 in sick patients [106],

nitric oxide synthase inhibitors with severe sepsis [107], G-CSF in septic patients [102], omeprazole suspension [109, 110] and an in-line heat moisture exchange filter and heated water humidifiers in patients on ventilators. There is also therapy that may be controversial when used in all ICU patients but may be useful in certain situations. This includes selective gut decontamination, which can be very valuable in acute liver failure, burns, and pancreatitis [111, 112]. Inhaled nitric oxide may help certain patients with ARDS, particularly after pulmonary resection [113-115]. Intra-operative maintenance of tissue perfusion may prevent ARDS in surgical patients [116, 117]. A protective ventilation strategy may help improve weaning. Lexipafant (a platelet-activating factor antagonist) may help with acute pancreatitis [118]. Veno-venous hemofiltration may help some septic patients [119, 120]. Extracorporal life support may help with end-stage ARDS [121]. Partial liquid ventilation may help in trauma patients with severe lung injury. Avoiding hypothermia may decrease mortality with trauma and decrease wound infections in abdominal operations [122]. rBPI may help patients after liver resection [123]. Enalaprilat may improve gut perfusion in injured patients [124]. Selenium may improve clinical outcome and decrease acute renal failure after injury [125]. PGE_1 may decrease mortality in trauma patients [126]. Plasma G1inh, a complement inhibitor, may help some patients [127]. Ventilation with the prone position, kinetic therapy bed, and rotational therapy may improve ARDS [128]. Lysofylline will protect with Il-2 therapy and in bone marrow transplants [129]. Hypertonic 7.5% saline and/or 6% dextran 70 may be particularly helpful in resuscitation of head injury patients [130, 131]. Recombinant human erythropoietin can help patients with postoperative anemia [132]. Preoperative human recombinant interferon gamma will modulate operative immunosuppression [133]. Anti-oxidant supplementation may reduce the incidence of MODS [134]. Testosterone administration will decrease muscle metabolism in severe burns [135, 136]. Ornithine α-ketoglutarate will improve healing in severe burns [137]. Infusion of methylene blue helps patients with septic shock [138]. Intra-operative PGE_1 improves function of alveolar immune cells [139]. Prolonged ARDS can be helped by infusion of low dose corticosteroids [71].

Recombinant human growth hormone can be very useful in patients with the short bowel syndrome [140]. An example of using a substance (growth hormone) on everyone in the ICU and increasing mortality is the study by Takala et al. [141] Whereas Byrne et al. and others have shown clearly that growth hormone improves survival in severely burned patients [87]. Selective gut decontamination helped patients with acute pancreatitis [142], but was of no help when given to all trauma patients [143]. Avoiding ranitidine may decrease infection because of the effects of this drug [110]. rhG-CSF may be

helpful in septic patients with neutropoenia [108]. *N*-Acetylcysteine may help with acute lung injury [144].

A recent phase III trial of antithrombin III in sepsis suggested a beneficial effect in those not receiving heparin [145]. Platelet glycoprotein IIb/IIIa antagonists will reduce thrombin generation and improve flow after percutaneous coronary intervention [146]. High-dose intravenous immunoglobulins help prevent infection in multiple trauma patients [147] and in anergic patients undergoing cardiac operations [148]. Thus, specific therapy for specific abnormalities may be much more successful.

Conclusions

The complexities and variations in mediators in patients and in contributors to organ failure are impressive and important. They include: cytokine and receptor pleiotropy, polymorphisms and redundancy, cell-cell interactions, such as PMN and platelets, selectins, genetic variations in cytokine expression, individual differences in prior antigen exposure and immunity, population differences in various societies, gender gaps, aging, prior illness, and lifestyle influences.

These make comparisons and therapeutic trials difficult. Polymerase chain reactions may identify new pathogens and all SIRS may be infectious. New contributors to organ damage include: atherosclerosis due to infection, superantigen lethality, systemic *H. pylori* effects, cancer from infection, neutrophil activation and delayed apoptosis, mesenteric lymph effects, post-implantation inflammation, and host defense proteins – protegrins and defensins. Is signal transduction good, bad, or indifferent? If so, where and when? These contributors to organ failure must now be related to risk factors for MOF and to each other, and integrated with biology to better prevent MOF. Our task is formidable.

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