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Clinical Pharmacological and Therapeutic Considerations in General Intensive Care
A Review

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Contents

Summary

The application of clinical pharmacological concepts and therapeutic standards in intensive care settings presents particularly difficult problems due to the lack of adequately controlled background information and the highly variable and rapidly evolving clinical conditions where drugs must be administered and their impact evaluated. In this review, an attempt has been made to discuss the available knowledge within the framework of a problem-oriented approach, which appears to provide a more clinically useful insight than a drug-centred review.

Following a brief discussion of the scanty data and the most interesting models to which reference can be made from a pharmacokinetic point of view (the burn patient being taken as an example), the review concentrates on the main general intervention strategies in intensive care patients. These are based mainly on non-pharmacological measures (correction of fluid and electrolyte balance, total parenteral nutrition, enteral nutrition, oxygenation and ventilatory management) and are discussed with respect to the specific challenge they present in various clinical conditions and organ failure situations. In addition, 4 major selected clinical conditions where general management criteria and careful use

of prophylactic and therapeutic drug treatments must interact to cope with the variety of presentations and problems are reviewed. These include: acute cerebral damage; anti-infective prophylaxis and therapy; cardiovascular emergencies; and problems of haemostasis. Each problem is analysed in such a way as to frame the pharmacological intervention in its broader context of the underlying (established or hypothesised) pathophysiology, with special attention being paid to those methodological issues which allow an appreciation of the degree of reliability of the data and the recommendations which appear to be practiced (often haphazardly) in intensive care units. The thorough review of the published literature provided (up to mid-1986) clearly shows that in this field the quality of randomised controlled and epidemiological studies is rather unsatisfactory.

It would be highly beneficial to research and to clinical care if larger multicentric protocols and prospective epidemiological comparative investigations could be carried out to investigate more timely and adequately the variables which determine drug action, and the final outcome in the many subgroups of patients which must be considered in a proper stratification of intensive care unit populations.

This article has arisen from a series of joint research programmes of a group of clinicians working in general and highly specialised intensive care units, and a group of clinical pharmacologists interested in the assessment of what in their discipline really does matter in clinical practice (Bonati & Tognoni 1984; Farina et al. 1981; Tognoni et al. 1980).

From a clinical pharmacological point of view, intensive care may be seen as a situation where contradictory situations and facts are frequently met: for example, the use of many drug treatments primarily tested under non-intensive care conditions; the lack of formal evaluation of the interplay between pharmacological and non-pharmacological interventions which are often utilised side by side and not as components of an integrated management approach; the call for a better defined pharmacokinetic profile of drugs which are given mostly at constant dosage rates while the vital functions and the body compartments of the patient are rapidly changing; and the difficult challenge of defining standard conditions of care against which the specific role of a new intervention can be comparatively tested.

Following other attempts (Chernow & Raymond 1983; Majerus 1982), a systematic discussion of the problem is proposed with 3 main aims:

1. Consideration of the intensive care patient as one whose management needs most often take precedence over any search for a specific benefit to be derived from a particular pharmacological treatment: drugs are but one of the variables to be considered while pursuing a rational management programme.

2. Adoption of an approach that is tailored to the real-life situation of intensive care where patients are progressively and tentatively evaluated as their status is evolving, rather than assigned to a well-defined and stable diagnostic category. From this perspective, an approach where drugs are seen as specific tools aiming at specific targets loses its strength in favour of an attitude where active adjustment of therapeutic decisions and continuous evaluation are mandatory. This interplay is of course required in many other clinical situations; however, its importance in intensive care is underlined by the urgency of the situation and the uncertainty or unavailability of many pieces of information.

3. Consideration of intensive care as a situation where straight answers and guidelines must be accompanied by continual questioning and re-evaluation of the widely open methodological problems that exist behind 'recommended' treatments.

The rationale for selecting the topics to be discussed in this review lies in the reality of general intensive care units (ICUs) [Abizanda Campos et al. 1980; Farina et al. 1981; Merriman 1981]. Intensive perinatal or coronary care problems will not

Glossary of terms

ARDS
Acute respiratory distress syndrome: an acute respiratory failure and distress associated with a specific incident or illness with the exclusion of exacerbation of chronic lung disease (National Institutes of Health 1972)

F_iO_2
Inspired oxygen fraction. Oxygen in high concentration is required to maintain life during certain lung diseases, but it carries the risk of toxicity (Deneke & Fanburg 1982)

CMV
Controlled mechanical ventilation: a form of respiratory support in which gases are pumped into the patient's lung by a mechanical ventilator. The expiration is controlled by the ventilator but is most often passive

$\overline{Paw}$
Mean airways pressure (averaged for time during the respiratory cycle)

PEEP
Positive end-expiratory pressure: airways pressure is not allowed to decrease below a set value during expiration (Shapiro et al. 1983; Weisman et al. 1982)

IRV
Inverse ratio ventilation: a form of mechanical ventilation. Inspiration is greatly prolonged, giving high inspiratory time ratios (e.g. 4 : 1) [Baum et al. 1980]

IMV
Intermittent mandatory ventilation: a form of mechanical ventilation in which spontaneous breathing is permitted but supplemented by a limited number of mechanical breaths (Weisman et al. 1983)

HFPPV
High frequency positive pressure ventilation: a form of respiratory support in which the ventilator provides high ventilator frequencies (from 60/min to ∞) at relatively low tidal volumes (Sjöstrand & Eriksson 1980)

Differential lung ventilation
A form of mechanical ventilation by which each of the two lungs is ventilated independently according to its own physiological needs (Powner et al. 1977)

FRC
Volume of gas remaining in the lungs at end-expiration

TSLC
Total static lung compliance: the amount of gases that can enter the lung generating a unit change in pressure – a measure inversely related to lung stiffness

V_D/V_T
Physiological dead space: the portion of tidal volume that does not participate in gas exchange

Barotrauma
Damage to the lung due or related to an increase in airway pressure (e.g. pneumothorax); sometimes extended to the damage produced by high airways pressure on organs other than the lung (e.g. liver and kidney function impairment) [Johnson & Hedley Whyte 1972; Kumar et al. 1973]

be considered because the situations which are met in these settings are much better defined, provide a relatively easier ground for a positive interaction of clinical pharmacology and clinical care, and the literature related to specific drug therapies and clinical conditions is well developed and is covered periodically in careful reviews.

1. The Pharmacokinetic Approach to Intensive Care

The relationship of drug dosing and disposition to drug effects, efficacy and toxicity has been extensively investigated and documented and is readily available in comprehensive and easily accessible reviews, which are regularly updated (Gibaldi & Prescott 1983). From a systematic scrutiny of specialty journals in this area, it is easy to verify that while the information is abundant and often detailed for disease states where a single organ or system is impaired, the data on clinical conditions where multiple organ failure is the rule are rather scanty. This is also true with respect to prognostic and descriptive mathematical modelling. Such a finding is not unexpected, because of the obvious difficulties that are inherent in studies where animal models mimicking complex clinical conditions are not readily available (Bortolotti & Bonati 1985) and which would require a close and long term interaction of clinical pharmacologists with intensive care clinicians to produce enough data to represent reliably the reality of intensive care patients or populations.

Possibly the most comprehensive model for what could be an optimum approach to complex situations is described in a series of publications on burns patients, where cardiovascular, hepatic, renal and dermatological functions are contemporaneously involved (Sawchuk 1984; Sawchuk & Rector 1980). The major pathophysiological functions which are affected and their pharmacokinetic implications are summarised in table I. The rapid changes of clinical status can be associated with variations in the disposition of drugs. In the case of drug protein binding, it is clear that the same variable may be affected differently according to

Table I. Major pathophysiological functions affected in burns patients and their pharmacokinetic implications (after Sawchuk 1984)

Physiological function	Pathological status	Pharmacokinetic variables changed
Cardiovascular	↓ Cardiac output during the early hours, then ↑ within 1-4 days ↓ Peripheral blood flow	Apparent volume of distribution Protein binding Metabolic clearance
Fluid balance	Oedema ↓ Albumin ↑ Bilirubinaemia ↑ Free fatty acids ↓ High-density lipoproteins ↑ Glycoproteins	Renal clearance Half-life Percutaneous absorption
Metabolic	↑ Catabolism → evaporative heat loss and ↑ catecholamine secretion ↓ Drug metabolising enzyme activity	
Renal	↓ Creatinine clearance Oliguria	
Epidermal	Destruction of epidermal strata	

the type of drug (acidic or basic), and the degree of control of the clinical condition in the various stages. Whereas a marked decrease in the serum concentration of albumin occurs, possibly leading to an increase in the free fraction of acidic drugs, the concentration of α_1-acid glycoproteins is increased, leading to increased binding of basic drugs (with consequent altered volume of distribution, serum concentrations and pharmacological effects [see Bowdle et al. (1980) for phenytoin, and Liebel et al. (1981) for *d*-tubocurarine]. However, these changes may be rapidly followed by normalisation of the situation when fluid and protein losses are compensated.

Along this line of reasoning, a comprehensive approach has also been proposed for cardiovascular emergencies (see review by Pentel & Benowitz 1984). This review is very exhaustive and should be referred to both for its methodology and the specific information it provides.

2. General 'Background' Conditions and Treatments

2.1 Fluid and Electrolyte Replacement Therapy

The general criteria and recommendations for fluid replacement therapy have been adequately reviewed (Shoemaker 1982) and will not be discussed here in detail. Precise measurement of fluid balance by weight is often clinically impracticable and must be based on information available from haemodynamic assessments, haematocrit values (also influenced by bleeding as well as fluid loss), haematocrit/Na^+ ratio, plasma and urine osmolarity, and the urinary Na^+/K^+ ratio.

Considerable controversy still exists regarding the optimum fluid replacement schedule in shocked patients when adult respiratory distress syndrome (ARDS) is either feared as a complication or has already developed. The inconsistency of the available data could possibly be a consequence of the uneven quality and comparability of the clinical material represented in most publications (table II), where different therapeutic end-points may have been aimed at (e.g. normalisation of diuresis, systemic arterial pressure, central venous pressure or pulmonary artery wedge pressure). The following discussion is advanced as a possible basis for a consensus on fluid replacement policy.

2.1.1 Fluid Replacement in Patients at Risk for ARDS

1. *Young patients who are in a satisfactory general condition but hypovolaemic, or in a very early phase of shock:* volume replacement therapy can be equally efficaciously and safely based on either crystalloids or colloids; however, a slower haemodynamic normalisation may be expected and a higher water and salt input is required with crystalloids.

2. *Older patients in a similar clinical condition, presenting with cardiac, renal or pulmonary prob-*

Table II. Volume expanders in shock: profile from prospective and retrospective studies

Reference	Clinical condition	Treatment	Results/comments
Colloids harmful			
Lucas et al. (1979, 1980) Dahn et al. (1979) Johnson et al. (1979)	Polytrauma	Blood + ↓ 120 ml/h crystalloids for 28 hours ↕ 96 ml/h for 5 days *or* 125 ml/h for 37 hours 5 ml/h for 5 days + 150g albumin/day	Colloids are associated with: delayed and decreased elimination of fluids trapped in third space negative inotropic effect ↑ pulmonary oedema and ↑ MV ↑ post-surgical bleeding
Colloids equally effective as crystalloids			
Virgilio et al. (1979) Lower et al. (1979)	Aortic surgery	RL Albumin 5% in RL Amounts according to haemodynamic monitoring PRC if needed	Colloids are associated with infusion of smaller volumes No differences in: mortality morbidity lung function *vs* MV
Crystalloids harmful			
Jelenko et al. (1979) Boutros et al. (1979) Haupt & Rackow (1982) Shoemaker et al. (1981)	Burns Abdominal vascular surgery	Various treatment with: saline, DW5, RL, albumin 5% in RL *vs* hetastarch	Colloids are associated with: infusion of smaller volumes earlier normalisation of haemodynamic and renal functions

Abbreviations: DW5 = 5% dextrose in water; RL = Ringer's lactate; PRC = packed red cells; MV = mechanical ventilation.

lems: colloids are a better choice to allow a swifter haemodynamic stabilisation and a lower water and salt load.

3. *Patients in whom sepsis is the underlying cause of hypovolaemia, and young patients with advanced or very severe traumatic shock:* colloids are again the first choice. In these conditions an increased permeability of the arteriolar-capillary (mainly pulmonary) membrane can be expected within 24 to 48 hours of the acute event. As particular attention must be paid to haemodynamic colloidal-osmotic equilibria, volume replacement should be assured with the smallest possible volume of crystalloids and albumin. The colloid osmotic pressure (COP) should never be lower than 17mm Hg (Morussette et al. 1979) and the colloid osmotic pressure-pulmonary artery wedge pressure difference must not fall below 6mm Hg (Weil et al. 1979).

In general, colloids (dextran or hetastarch) that are similar to albumin in molecular weight and in their preferential distribution in the intravascular compartment (Dawidson et al. 1980; Grundmann & Meyer 1982; Haupt & Rackow 1982) are the preferred choice. When artificial colloids are used, careful monitoring of the colloid osmotic pressure is essential to avoid the risk of hypervolaemia leading to interstitial oedema. Neither for albumin nor for artificial colloids has the water and salt retention reported by Lucas et al. (1980) been confirmed (Haupt & Rackow 1982).

2.1.2 Fluid Replacement in Patients with ARDS

The criteria for fluid replacement therapy in patients with acute respiratory distress syndrome are even more controversial. According to some authors (Lucas et al. 1980), colloids increase leakage from the interstitial space, where albumin binds to collagen, and impair lymphatic drainage. As a result, the interstitial colloid osmotic pressure rises, and the oedema of the alveolar-capillary membrane is worsened. An opposite view is centred around the role of albumin in sustaining the increase of intravascular colloid osmotic pressure: because permeability increases as a gradual and not generalised process, the interstitial fluid is 'dragged' in and allows re-expansion of the circulating volume, with a consequent lower requirement for water and salt loading, and a reduction of the risk of interstitial oedema (Pontoppidan et al. 1972; Wilson & Sibbald 1976).

While a reliable direct measure of the extent of the leakage is difficult to achieve, comparative trials of crystalloids *versus* colloids in ARDS patients support the second hypothesis showing that colloids definitely produce more satisfactory haemodynamic stabilisation with the smallest water and salt load (Appel & Shoemaker 1981; Hauser et al. 1980; Skillman et al. 1970). On the other hand, worsening of pulmonary function following excessive fluid loading is a well-known problem in severe ARDS (Appel & Shoemaker 1981). Colloids (whenever possible, albumin) appear to be the fluid of choice for haemodynamic stabilisation in 'extreme ARDS' (Gattinoni et al. 1980, 1983; Iapichino et al. 1983).

2.2 Total Parenteral Nutrition (TPN)

The justification for this section may be summarised as follows (Askanazi et al. 1980a; Baker et al. 1982; Baracas et al. 1983; Birkhahn et al. 1980; Clowes et al. 1980a, 1983; Kien et al. 1978; Long et al. 1977a,b; McMenamy et al. 1981a; Mullen et al. 1979; Stein et al. 1977):

1. There is a close relationship between the severity of acute injury (of whatever origin), energy demand and the dynamic balance of protein synthesis and catabolism (nitrogen balance).
2. An uncorrected depletion of amino acids from the muscular, pulmonary and immunological reservoirs is likely to be associated with the development of immunodepressed/infective states and therefore with an unfavourable overall clinical course of the critically ill patient.
3. An adequate anabolic response (positive or less negative nitrogen balance) through nutritional support is a prerequisite for a favourable outcome (Rapp et al. 1983).

Table III summarises the experimental and clinical evidence for the role of total parenteral nutrition in assuring a favourable nitrogen balance by minimisation of the loss of proteins which are critical to assure essential physiological functions, and by control of catabolism and stimulation of anabolism. The present state of knowledge about the reciprocal role of calories and nitrogen (Bozzetti 1976; Elwyn et al. 1979; Iapichino et al. 1985; Jeejeebhoy 1977; Shizgal & Forse 1980) can be summarised as follows:

a) At every caloric intake, the nitrogen balance improves with nitrogen supplementation
b) Conversely, at every nitrogen intake, increased caloric support favours a better nitrogen balance
c) Glucose or mixed glucose and lipid sources of calories can be considered equivalent in favouring nitrogen utilisation in depleted patients, at least after an adaptation phase (Bark et al. 1976; Jeejeebhoy 1977; Macfie et al. 1981; Shizgal & Forse 1981). However, in the acute post-traumatic phase, a mixed glucose and lipid intake is associated with a worse nitrogen balance than is the case with an equivalent glucose intake (Freund et al. 1980; Long et al. 1977a; Shizgal & Forse 1981; Woolfson et al. 1979).

Calorie and nitrogen requirements differ according to both the needs of the individual patient and the target nitrogen balance. For example, in depleted non-catabolic patients, the main therapeutic goal is building of the lean mass (nitrogen balance +2 to +4 g/day): this will require 0.15 to 0.25g nitrogen/kg plus 40 to 60 non-protein kcal/

Table III. Experimental and clinical evidence for the role of total parenteral nutrition (TPN) is assuring a favourable nitrogen balance by minimisation of protein loss and by control of catabolism and stimulation of anabolism

Experimental situation	No. of patients	Function investigated	Treatment	Results	References
Injury produced in:					
normal rats		Muscular, pulmonary protein turnover		↑ Synthesis *vs* pre-injury	Stein et al. (1977)
starved rats		Muscular, pulmonary protein turnover		↓ Synthesis *vs* pre-injury	Stein et al. (1977)
normal rats		Muscular protein turnover	Glucose	↓ Muscular catabolism	Moldaver et al. (1980)
normal rats		Muscular and visceral protein turnover	Aminoacids	↑ Synthesis	Moldaver et al. (1980)
Post-surgery	4	Body catabolism	Glucose + insulin	↓ Overall catabolism	O'Keefe et al. (1981)
and trauma	22				Woolfson et al. (1979)
	19				Iapichino et al. (1982)
Trauma and sepsis	1	Metabolic balance, splanchnic protein turnover	Aminoacids	↑ Protein synthesis	McMenamy et al. (1981b)
Post-surgery	5	Protein turnover	Aminoacids	↑ Visceral synthesis = overall catabolism	O'Keefe et al. (1981)
	4	Protein turnover	Aminoacids + glucose + insulin	↑ Visceral synthesis ↓ Overall catabolism	O'Keefe et al. (1981)
Trauma	5				Long et al. (1977b)
	22				Woolfson et al. (1979)
	21	Nitrogen balance	Aminoacids + glucose + insulin	Improvement of negative nitrogen balance	Clowes et al. (1980b)
	18				Shenkin et al. (1980)
	19				Iapichino et al. (1982)
Trauma	14	Nitrogen balance + 3-methylhistidine	Aminoacids + glucose + insulin	Improvement of negative nitrogen balance ↓ Catabolism	Iapichino et al. (1985)

kg of actual bodyweight. On the other hand, injured patients require primarily control of the major catabolic nitrogen loss: in this situation a double amount of nitrogen (0.27 to 0.29 g/kg) plus 35 to 40 non-protein kcal/kg will favour a zero nitrogen balance (1IU of insulin added to each 4 to 8g fraction of glucose assures a better anticatabolic effect) [Iapichino et al. 1982; Woolfson et al. 1979]. The achievement of a positive nitrogen balance in the acute reaction phase is an unrealistic target (see below).

The role of specific aminoacids in injured and septic patients is still being investigated. Branched-chain aminoacids are essential to assure adequate synthesis of proteins in the liver (Blackburn et al. 1979; McMenamy et al. 1981b); their hormone-like action in controlling the rate of muscular catabolism is still controversial (Cerra et al. 1982; Freund et al. 1982; Schmitz et al. 1982). On the other hand, a reduced supply of aromatic and sulphurated aminoacids is recommended since their utilisation in the liver is impaired in septic conditions (Clowes et al. 1980a; Freund et al. 1979; Larson et al. 1982; McMenamy et al. 1981b; Smith et al. 1982).

2.2.1 Total Parenteral Nutrition in Acute or Chronic Pulmonary Insufficiency

A comprehensive definition of this condition would include all patients with impaired pulmonary gas exchange and partial carbon dioxide retention. The higher cardiovascular and respiratory demand may worsen a situation of acute respiratory insufficiency in spontaneously breathing patients with limited ventilatory capacity. Partial replacement of the glycidic load with lipids has been proposed to reduce the surplus production of carbon dioxide which follows the increased respiratory quotient (Askanazi et al. 1981). The key feature is an increased energy requirement stimulated by the caloric intravenous supply (Askanazi et al. 1980b; Gattinoni et al. 1974). This concept appears applicable in depleted patients with respiratory insufficiency where the protein-sparing effects of lipids are equivalent to those of carbohydrates; however, it is debatable in injured patients in whom lipids have been shown to have a lower protein-sparing effect when compared with glucose alone. Hence, to achieve the same nitrogen balance, a higher caloric intake will be required when using lipids (Jarnberg et al. 1981).

In summary, the present state of knowledge underlines the importance of avoiding caloric loads higher than those strictly required for a zero nitrogen balance (a positive nitrogen balance must be discouraged) [Iapichino et al. 1983]. Optimisation of the nitrogen balance should be sought through increased nitrogen intake, provided due attention is given to the increased metabolic demands (Askanazi et al. 1982).

2.2.2 Total Parenteral Nutrition in Acute Renal Failure

This clinical condition which follows shock, trauma or sepsis is characterised by an altered fluid, electrolyte and acid-base status, as well as by hypercatabolic activity which can lead to an impaired nutritional condition and high morbidity and mortality.

The suggested treatment of the nutritional deficiency is based on a nitrogen intake tailored to match the losses. Any type of aminoacids coupled with at least 35 to 40 kcal/kg may be used: unlike the situation in chronic renal insufficiency, urea recirculation is not clinically relevant (Lee 1980).

This approach modifies the classic Giordano total parenteral nutrition schedule for acute renal failure. It must be noted, however, that the few randomised studies which have addressed this issue (Kopple & Feinstein 1983) have not confirmed the superiority of a free nitrogen input (15g nitrogen composed of equal parts of essential and non-essential aminoacids) over the 2 to 3g nitrogen essential aminoacids only regimen, in improving nitrogen balance and survival. No definite criteria can therefore be set for the choice and clinical use of branched-chain amino- or ketoacids to assure optimum catabolic control.

The caloric component can be assured with glucose or glucose-lipid mixtures, provided no more than 1 g/kg of lipids is given at a slow infusion rate to allow for their reduced elimination (Druml et al. 1982).

2.2.3 Total Parenteral Nutrition in Liver Failure

In acute, toxic and infectious liver conditions, the aim of nutritional support is dual (Fischer 1981):

1. To reduce the release from muscles of aminoacids the liver cannot metabolise (glucose and insulin are effective); and
2. To re-establish the plasma balance of branched-chain and aromatic aminoacids by infusion of branched-chain aminoacids.

In chronic, severe hepatic insufficiency, nutritional therapy can play a more important role. In patients with hepatic encephalopathy, it is currently recommended (Fischer 1981) that a 24- to 36-hour infusion of high-dose branched-chain aminoacids be given to waken the patient, followed by supportive nutritional therapy based on glucose and aminoacids (60 to 70 g/day, mainly branched-chain aminoacids to avoid worsening or precipitation of encephalopathy which may occur with aromatic and sulphurated components). The awakening effect of branched-chain aminoacids in this situation is supported by data obtained from ex-

perimental models (Higashi et al. 1981; Smith et al. 1978) and from uncontrolled clinical trials (Fischer et al. 1974, 1976); however, the results from controlled clinical trials are more doubtful (James et al. 1979; Michel et al. 1980; Wahren et al. 1981). Furthermore, the overall efficacy of the treatment seems to be restricted to an improvement of the general clinical status. No long-lasting benefit can be claimed with respect to brain function and survival (Eriksson & Wahren 1982).

2.3 Enteral Nutrition

The aims and terms of reference for the metabolic aspects of enteral nutrition are the same as for total parenteral nutrition (with which enteral nutrition is often combined) and will not be discussed here. Enteral nutrition has acquired an increasing role in almost all severe (Kaminski 1976; Luc et al. 1981) and even extreme (Iapichino et al. 1983) clinical conditions, for 2 reasons:

1. The development of techniques, devices and products which ensure adequate and easily manageable nutritional intake; and
2. A better understanding of the physiological and biochemical mechanisms underlying enteral absorption of the various components of a diet.

Given as an oral meal, enteral nutrition is an integration of a free diet which cannot assure more than 80% of the body's caloric and protein needs. Given through a nasogastric tube, it may represent the only source of nutritional support or an effective complement to total parenteral nutrition. This latter combination reduces both the water load of enteral nutrition, and total parenteral nutrition-related complications, and is specifically useful for oliguric, cardiac, ARDS and head injury patients.

2.4 Oxygenation and Ventilatory Management

Adequate oxygenation is often a critical issue for the intensive care clinician. There is no doubt that low arterial oxygen levels are extremely dangerous in acute situations: 'hypoxia not only stops the machine, it also destroys the machinery.'

Ventilatory management is still the cornerstone of therapeutic intervention in intensive care patients. The provision of a viable gas exchange represents the immediate therapeutic target, but undoubtedly healing of lung lesions and prevention of damaging effects upon other organs remain the ultimate goals and the ones which should always receive maximum attention.

ARDS can be taken as the model of a relevant clinical condition where the problems of respiratory care can be discussed. In ARDS lungs, the normal matching of ventilation and perfusion is greatly altered. Under these conditions, the necessary adequate compromise between oxygenation and CO_2 clearance may require extremely unphysiological interventions, often demanding high minute volume ventilation (sometimes in excess of 20 L/min), high airways pressures, and high inspired oxygen fractions (F_iO_2). As there is often no specific treatment available for ARDS, management is confined merely to life-supportive intervention (Gattinoni et al. 1983).

2.4.1 Rationale and Risk/Benefit Profile of Mechanical Ventilation

Mechanical ventilation was introduced to support the breathing of patients with neuromuscular disease and those undergoing paralysis anaesthesia. Its use soon spread to the treatment of what was later to be called ARDS.

It must be emphasised that the mechanical ventilator is not primarily an oxygenator, but rather a mechanical pump that removes CO_2 from the natural lung. However, oxygenation does not require ventilation, as anaesthesiologists have long shown with the apnoeic oxygenation technique (Frumin et al. 1959). Table IV provides an overview of the pros and cons to be expected from some of the available ventilatory management measures, while figure 1 summarises the pathophysiology involved in the main aspects of respiratory support, focusing on improvement of oxygenation. It is important to note that the only relevant benefit brought about by controlled mechanical ventilation (CMV) is the relief of respiratory work, as long as it does not induce muscular atrophy and discoordination.

The role of CMV is diminishing as ventilatory

Table IV. Advantages and disadvantages of some of the available ventilatory management measures

Intervention	Effect or target	Side effects
Spontaneous breathing, IMV (Weisman et al. 1983)	Prevent deterioration of respiratory mechanics Improve gas and pressure distribution within the lungs	Increased respiratory work and body oxygen consumption Patient discomfort Rapid shallow breathing induces atelectasis
Controlled mechanical ventilation	Replace the function of respiratory control centres Prevent respiratory fatigue Decrease body $\dot{V}O_2$, $\dot{V}CO_2$ Increase $\overline{Paw}$ Complete control of airways pressure Easy control of F_iO_2 and humidification	Need for sedation Respiratory muscle atrophy and discoordination Increased V_D/V_T Increased barotrauma Decreased cardiac output and renal function (Marshall et al. 1982)
PEEP (Shapiro et al. 1983; Weisman et al. 1982) Increased $\overline{Paw}$ (Boros et al. 1977)	Increase alveolar recruitment Increase lung volume Improve oxygenation	Increased V_D/V_T Increased barotrauma Decreased cardiac output and renal function (Marshall et al. 1982)
Increased F_iO_2	Correct local alveolar hypoxia in low VA/Q areas Increase the oxygen content of blood	Oxygen toxicity (Deneke & Fanburg 1982) Atelectasis (denitrogenation) [Dantzker et al. 1975]

management is becoming more a combination of specific therapeutic interventions, with preset physiological goals. Thus, CMV has become a specific measure for patients in whom CO_2 clearance cannot be safely reached by other means. It is often possible to combine two or more manoeuvres to reach a specific goal, e.g. positive end-expiratory pressure (PEEP) plus CMV is called controlled positive pressure ventilation (CPPV), offering the advantages (and disadvantages) of the two.

As is often the case in intensive care medicine, the therapeutic manoeuvres indicated for ARDS carry a high rate of side effects. At present, the iatrogenic effects of therapy upon the course of the lung disease cannot be clearly separated from the natural history of ARDS (Pratt et al. 1979). On the other hand, respiratory therapy is a mandatory, life-supporting measure without which ARDS can progress to a full-blown situation. Hence, even when trying to abstain from an F_iO_2 higher than 0.4 to 0.6 and from higher than normal airways pressures (20cm H_2O PEEP), we are sometimes left with no other choice than to resort to more dangerous settings to ensure viable blood gases. The frustrating exercise of balancing advantages and disadvantages of any specific intervention should always be performed. Unfortunately, little is known about the long term effects of respiratory treatment upon other systems. It is not uncommon for ARDS patients to die not from hypoxaemia, but from failure of other organs or systems (Kirby et al. 1975) whose function may have been severely affected by the respiratory therapy.

3. Management of Selected Intensive Care Conditions

3.1 Acute Cerebral Damage

3.1.1 General Pathophysiological Considerations

Acute cerebral damage due to focal traumatic, non-surgical lesions has been chosen as the reference clinical condition for a discussion of the basic principles (pathophysiological mechanisms and criteria for pharmacological treatment) involved in formulating a rational clinical pharmacological ap-

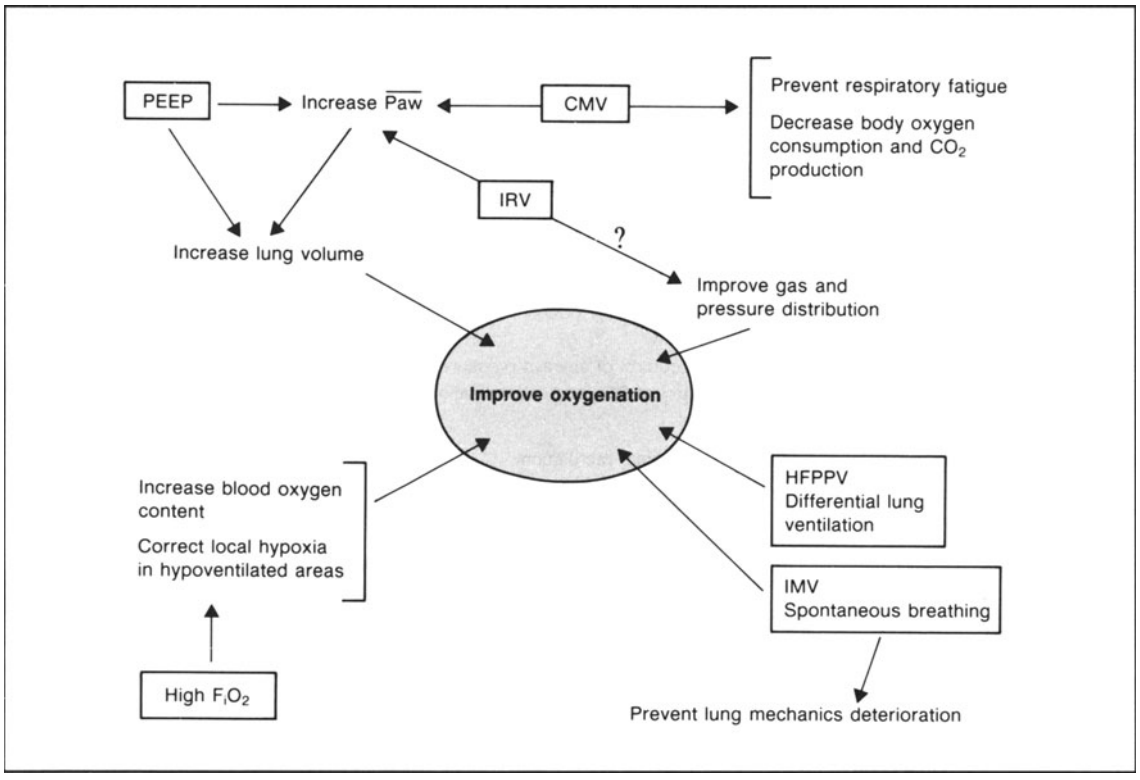

Fig. 1. The pathophysiology of respiratory support. Main therapeutic interventions shown in boxes. *Abbreviations*: PEEP = positive end-expiratory pressure; CMV = controlled mechanical ventilation; IRV = inverse ratio ventilation; $\overline{Paw}$ = mean airways pressure; HFPPV = high frequency positive pressure ventilation; IMV = intermittent mandatory ventilation; F_iO_2 = inspired oxygen fraction.

proach to intensive care situations with major involvement of the central nervous system (CNS). However, the points made here have a broader application to cerebral lesions frequently occurring in intensive care settings that are caused by other noxae such as focal vascular injury, acute infections and tumours.

The basic processes leading to acute cerebral damage can be described by the scheme shown in figure 2. The hyperaemic swelling and ischaemic focal cerebral oedema cause a high intracranial pressure (ICP). Focal oedema leads to cerebral shift; the displacement of the brain from its axis against the tentorium and the falx leads to cerebral ischaemia and oedema. The resulting diffuse oedema further increases the intracranial pressure and the ischaemic anoxic damage (Bruce et al. 1981; Clifton et al. 1983; Cold & Jensen 1978; Miller 1985; Obrist et al. 1984; Overgaard & Tweed 1983).

3.1.2 A Problem- and Treatment-Oriented Framework

The variables listed in figure 2 may be amenable to prophylactic and therapeutic treatment according to the following sequence, which serves as a guide for discussion of the most promising, albeit controversial, approaches to the management of acute cerebral damage:

1. Prophylaxis and treatment of the causes of secondary cerebral damage (worsening factors)
2. Avoiding or minimising cerebral oedema and ischaemic anoxic damage
3. Symptomatic therapy of high intracranial pres-

sure if the above 2 measures fail
4. Preservation of cardiovascular, respiratory and metabolic haemostasis
5. Avoiding iatrogenic problems of late complications
6. Early rehabilitative procedures.

Prophylaxis and Treatment of Worsening Factors

The primary goal of the management of acute cerebral damage is to control all factors which could worsen the cerebral lesion. Table V schematically sets out the clinical guidelines to be followed.

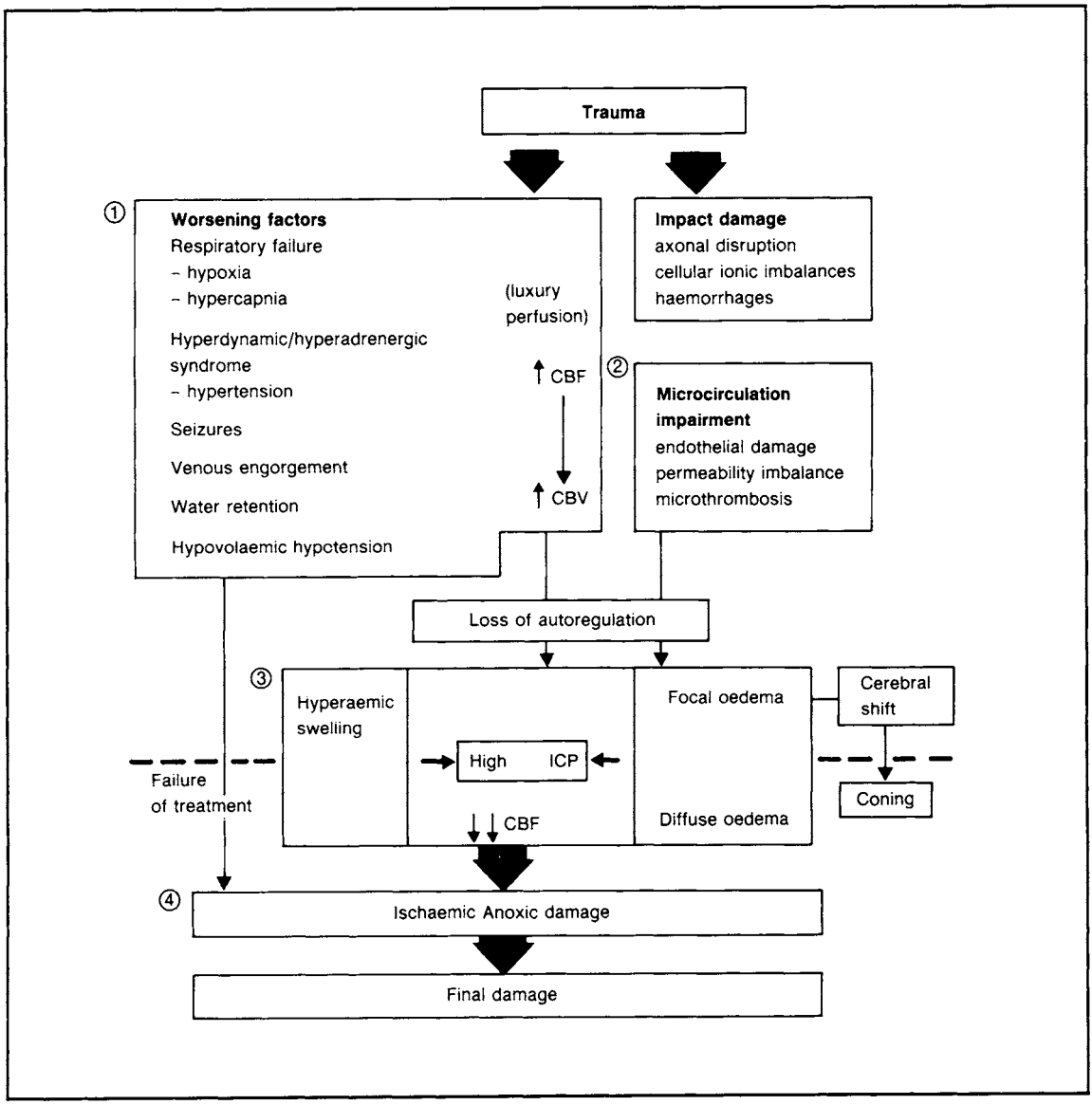

Fig. 2. The pathophysiology of acute traumatic focal lesions: CBF = cerebral blood flow; CBV = cerebral blood volume; ICP = intracranial pressure; Hypercapnia → acidotic vasodilation; Hypoxia → lactic acidosis-vasodilation; Venous engorgement - from cerebral coning, head malposition, high endothoracic pressure, etc.

Table V. Prophylaxis and treatment of worsening factors in acute cerebral damage

Worsening factors	Available treatments	Comments
Hypoxia Hypercapnia	Oxygen Mechanical ventilation	Airways patency and O_2 supplementation are mandatory; mechanical ventilation only in cases of respiratory failure, deep sedation or therapeutic hyperventilation
Hypotension	Intravenous fluids Vasopressure drugs	Fluid overload may increase cerebral oedema
Hyperadrenergic-hyperdynamic syndrome Hypermetabolism Pain-straining Decerebrate-decorticate fits	Antiadrenergic drugs (1) Sedatives (2) Analgesic drugs (2) Muscle relaxants (3)	1. Efficacy not proven. The choice depends on an evaluation of the expected benefit/risk profile in each case. The dose of *β-blockers* should be carefully titrated according to the severity of the clinical conditions *Clonidine* IV bolus (see table IX) may cause mild sedation, hypotension, bradycardia but not respiratory depression 2. Barbiturates (see table VIII); chlorpromazine may activate an epileptic focus and may be highly hypotensive 3. Curarisation may mask a neurological state; the systemic venous and lymphatic drainage is impaired
Early seizures	Anticonvulsant drugs	*Treatment:* 'fast-acting drugs' (IV diazepam, or barbiturate) + loading dose of phenytoin (15 mg/kg IV or phenobarbitone (20 mg/kg IV drip) *Prophylaxis:* no 'recommended' treatment schedule is available as yet

a This table should be read with strict reference to: (a) table VIII, where the protection from ischaemic-anoxic insults, and the prophylaxis and treatment of high intracranial pressure are discussed; and (b) section 3.1.2 (cerebral oedema).

The hyperdynamic/hyperadrenergic syndrome (table VI) may be seen as an exaggeration or caricature of the classical 'fight or flight' reaction; it is also seen in the narcotic 'withdrawal syndrome'. A hyperadrenergic state is the common feature of these conditions. In patients with acute cerebral damage this may be due to the functional disconnection of the brainstem from the hemispheres or to a direct stimulation of the diencephalic-hypothalamic-brainstem system as a result of high intracranial pressure, ischaemia, blood leaking into the CSF, pH changes in the CSF, etc. (Pia 1974), as well as extracranial causes. Therapy and prophylaxis of this syndrome rest upon the rather unspecific use of various classes of sedatives and of antiadrenergic drugs. Although their mechanisms of action are different and the treatment schedules are far from well established, all the drugs listed in table V have an unspecific 'sedative' effect, permit good control of the increased muscular tonus and of decerebrate-decorticate fits, and contribute to the reversal of the systemic and cerebral circulatory and metabolic alterations.

Seizures: Convulsions are frequent and very dangerous in acute cerebral damage. Effective prophylaxis is not easy because of the short interval between injury and the first post-traumatic seizures. Standard treatment is based on the classical anticonvulsant drugs, as shown in table V. Though almost universally accepted, the efficacy of prophylaxis has never been proven in formal trials (Young et al. 1983). The dosage schedules pose an interesting clinical pharmacological problem, as early 'effective' drug concentrations do not seem to be easily defined or achievable, even when high loading doses are used. Moreover, it is clear that the prophylactic benefit could be the result of the various measures included in the overall management scheme rather than of a specific pharmacological prophylaxis.

Table VI. Chain of local and systemic events resulting from the hyperadrenergic syndrome and seizures

Hyperadrenergic-hyperdynamic syndrome	Seizures
Central level ↑ CBF ---▶ ↑ CBV → cerebral oedema → ↑ ICP → ↓ CBF **Systemic effects** Hypertension, tachycardia, arrhythmias, raised cardiac output Hyperventilation, pulmonary VA/Q imbalance, pulmonary oedema Piloerection, sweating Catabolism Hyperthermia Increased antidiuretic hormone secretion Increased muscular tonus?	**Central events** ↑↑ $CMRO_2$ → ↑↑ CBF with 'luxury' perfusion and eventually neuronal hypoxia Vasodilation Abolished autoregulation? Ionic and neurotransmitters imbalances **Systemic effects** Hypoxia Hypercapnia Hyperadrenergic syndrome Muscular lactic acidosis

Abbreviations: CBF = cerebral blood flow; CBV = cerebral blood volume; ICP = intracranial pressure; $CMRO_2$ = cerebral metabolic rate for oxygen; VA/Q = ventilation to perfusion ratio.

Control and Prevention of Cerebral Oedema

Available knowledge on commonly adopted treatment for cerebral oedema is rather inconsistent. The standard regimen of corticosteroids for 3 to 4 days is based on theoretical considerations and suggestive experimental data, but has never been confirmed in properly controlled clinical trials (Braughler & Hall 1985) [table VII]. Positive results in other clinical conditions such as peritumoural and encephalitic oedema are hardly transferable to traumatic acute cerebral damage. A cornerstone of the treatment is the control of hyperaemia, a key causal factor in oedema. While there is at present no effective method for influencing the 'luxury flow' locally, antiadrenergic drugs (see table V) can help by reversing the hyperdynamic state (Clifton et al. 1983). This treatment requires careful circulatory, respiratory and EEG monitoring but compares favourably in terms of unwanted effects and nursing requirements with other treatments aiming at the same goal, such as barbiturate-induced coma or protracted mechanical ventilation (see below).

Control of High Intracranial Pressure

From figure 2, it is clear that the intracranial pressure depends on the type and the severity of the various factors which constitute the clinical condition of acute cerebral damage (Shapiro 1975). However, intracranial pressure monitoring (itself not a completely safe or reliable invasive technique) has failed to assess the relationship, if any, between intracranial pressure, the severity of cerebral damage, computerised tomography scan images, and the outcome. The threshold itself for treatment is not well defined.

Nevertheless, immediate and aggressive therapy is indicated on clinical grounds in the presence of cerebral shift and when cerebral coning is impending. The intervention strategy is summarised in table VIII (Quandt & de los Reyes 1984). Osmotic diuretics are the treatment of choice in the acute phase to reduce rapidly the extravascular water by increasing plasma osmolality. However, their prolonged use is best avoided; osmotic diuretics accumulate in the brain across a damaged blood/brain barrier, reversing the osmotic gradient, with a potential oedema-promoting effect. They also disturb the fluid and electrolyte balance, which must be the real target of prolonged and meticulous control. Frusemide (furosemide) may be useful in order to prevent the initial temporary hypervolaemia caused by osmotic diuretics and to reduce CSF formation.

Mechanical hyperventilation can reduce intracranial pressure in a few seconds by hypocapnic vasoconstriction and, in part, by decreasing cardiac

Table VII. Results of trials of corticosteroids in head injury patients

References	Treatment	No. of patients	Results	Comments
Gobiet et al. (1976)	No steroids	35	↓ mortality	Retrospective study
	Low doses[a]	24	↓ high ICP frequency	
	High doses[b]	34	↓ complications in high-dose group	Only patients with high ICP > 50mm Hg
Gudeman et al. (1979)	High doses[b] *versus*	20	No effect on outcome	Retrospective study Delay of 12 hours for high doses
	Low doses[a]	262	↑ complications	
Pitts & Kaktis (1980)	Placebo	18	No control of ICP	Prospective randomised study
	Low doses[a]	22	No increase of complications	
	High doses[c]	36		
Cooper et al. (1979)	Placebo	27	No effect on outcome	Prospective, double-blind study 35% focal lesions; 65% diffuse lesions
	Low doses[a]	25		
	High doses[b]	24		
Saul et al. (1981)	No steroids	50	No effect on outcome	Prospective, randomised study
	High doses[b]	50	The effect may be different for selected groups	
Braakman et al. (1983)	Placebo	80	No effect on survival rate and outcome	Prospective, double-blind study Comatose patients
	High doses	80		

a Low doses = 16 mg/day dexamethasone (or equivalent methylprednisolone).
b High doses = 100 mg/day.
c 24 mg/day.
Abbreviation: ICP = intracranial pressure.

output via positive intrathoracic pressures. Both mechanisms quickly fade, the former because of the restoration of normal cerebral pH, the latter because of compensatory water and salt retention (Heffner & Sahn 1983). Barbiturate-induced coma has been proven to reduce high intracranial pressure in some patients unresponsive to mechanical hyperventilation, osmotics, corticosteroids and CSF drainage (Marshall et al. 1979a,b; Rockoff et al. 1979). Interestingly, the pharmacokinetic behaviour of the most frequently studied drug, pentobarbitone, has only very recently become the object of specific interest (Bayliff et al. 1985). Repeated barbiturate doses are associated both with diagnostic problems and various systemic complications (e.g. hypotension, infections, bedsores). As severe cardiovascular depression is possible, the use of barbiturates calls for simultaneous monitoring of intracranial pressure and blood pressure in order to maintain a safe cerebral perfusion pressure. Since the reduction of intracranial pressure produced by these agents is related to a decrease of the cerebral metabolic rate for oxygen ($CMRO_2$) and a consequent decrease of cerebral blood flow (CBF) and cerebral blood volume (CBV), no further effect can be expected when metabolism is severely depressed and a 'burst suppression' pattern on the EEG is achieved (Kassell et al. 1980). Moreover, only the evoked potentials are useful when testing the neurological state in barbiturate-induced coma.

When cerebral compliance is critical, bolus doses of sedatives can be of benefit to prevent the increase of intracranial pressure in response to stimulating procedures (Moss et al. 1983); in these cases, EEG monitoring can be useful to predict their effect on intracranial pressure and cerebral perfusion pressure (Bingham et al. 1985). The persistence of

a high intracranial pressure, in the absence of surgically treatable lesions, means that treatment has failed, either due to inadequacy or delay.

Cerebral Protection

Table VIII summarises the goals (and the state of knowledge about the means to achieve them) of this strategy, which can be defined as 'a safe means of increasing the brain's tolerance to the anoxic-ischaemic insult' (Cohen 1981).

Despite the relatively long series of attempts centred on this procedure, it is still largely idealistic. Barbiturate-induced coma therapy, which has received much experimental and clinical attention over the last few years, has been associated with good results in focal ischaemic anoxic lesions but not with respect to global cerebral damage (Safar 1980). The overall rationale of an intervention which assigns beneficial effects to a reduction of the metabolic rate is under revision, as the functional metabolic rate is often already depressed in these patients (Astrup 1982).

As other experimental suggestions have failed in clinical trials, prevention and treatment of brain ischaemia remains a frustrating and unresolved clinical problem (Hinds 1985).

Table VIII. Prophylaxis and treatment of high intracranial pressure and measures for cerebral protection

Strategy	Available treatments	Comments
High intracranial pressure		
To normalise the intravascular volume		
↓ CBF	Mechanical hyperventilation	Effect is transient; risk of pulmonary infective complications
↓ $CMRO_2$ → ↓ CBF	Sedative and anaesthetic drugs	*Pentobarbitone* or *thiopentone* IV drip or boluses, 3-5 mg/kg to obtain a normal ICP or a burst suppression, pattern on the EEG (25-35 mg/L blood concentration). See text IV boluses of *lignocaine* (lidocaine): may cause hypotension, cardiac depression, seizures The benefit/risk profile of opiates, benzodiazepines, phenytoin is far from clear
↑ cerebral venous drainage	Head-up position Muscle relaxants	
To lessen extravascular water in non-damaged brain	Osmotic diuretics Fluid restriction	Bolus of *mannitol* (20%) 1 g/kg IV via a central line in case of impending coning (10% glycerol has the same osmotic power, but may cause hyperglycaemia and metabolic acidosis) Prolonged treatment is advisable only if ICP monitoring and careful control of fluid and electrolyte balance is assured
↓ CSF formation	'Loop' diuretics	Avoid hypovolaemia (to avoid ↑ catecholamines and ↑ ADH)
Cerebral protection		
To avoid or minimise ischaemic-anoxic damage	[Hypothermia]	Despite its proven efficacy, it is no longer used because of its unfavourable risk profile
Metabolic inhibition	Pharmacological coma	High doses of *pentobarbitone* or *thiopentone* by IV drip. Available results from major trials suggest that, if any, a benefit should be sought and tested in selected subgroups
Membrane protection	? Ca^{++} antagonists	Pending evaluation of *lidoflazine* 1 mg/kg by IV drip in global cerebral anoxia

Abbreviations: ICP = intracranial pressure; CBF = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate for oxygen; ADH = antidiuretic hormone.

Trends and Perspectives in Management of Acute Cerebral Damage

Over the last few years, new therapeutic strategies have been based on suggestions arising mainly from the availability of new technological tools which may provide a better insight into the morphological, metabolic and vascular aspects of acute cerebral damage. Relatively little has been done to exploit a parallel body of knowledge on neurotransmitters, which has grown significantly, but which up until now has resulted only in rather non-specific applications. Table IX summarises current knowledge of the effects of two recently emergent drugs in this area, clonidine and naloxone. The interactions of suggestive clinical evidence, pharmacological and biochemical background, and pathophysiological hypotheses indicate the probable path of clinical pharmacology over the next few years in this field.

3.2 Anti-Infective Prophylaxis and Therapy

It is a commonly accepted view that infections play a major role in the morbidity and mortality profile of intensive care patients (more than 50% of fatalities after the first week of intensive care unit stay are associated with infectious complications) [Allgöwer et al. 1980; Machiedo et al. 1981; Pottecher et al. 1979]. It is also well known that anti-infective (mainly antimicrobial) therapy accounts for the greater part of the most frequently prescribed drugs (Buchanan & Cane 1978; Farina et al. 1981).

While the importance of appropriate antimicrobial treatment in improving survival in many critical care conditions is undisputed, an analysis of the studies in this field (table X) suggests a situation where non-pharmacological factors are in the forefront. Where mentioned, antibiotic prophylaxis or treatment appears mostly as an accessory in descriptive and controversial analyses of hard-to-compare measures applied in widely differing settings. Sufficient prospective, properly stratified data (according to the various clinical and environmental variables) are not available to support a well-defined strategy and, even less, specific drug treatment. It is interesting that one of the most optimistic reports which documents the critical role

Table IX. Emerging trends in management of acute cerebral damage

Pharmacology	Clinical indications	Effect profile in acute CNS damage
Clonidine (α_2-adrenoceptor agonist)	Hypertension Opiate withdrawal	Reduces cerebral blood flow in man (Bertel et al. 1983) Minimises spasticity and controls autonomic dysreflexia from spinal cord injury in cats (Naftchi 1982) Controls autonomic dysreflexia and spasticity in human spinal injury (Naftchi, unpublished results) Controls hyperdynamic syndrome, intracranial pressure and muscular hypertonus in head injured patients (Procaccio & Boselli, unpublished results)
Naloxone (opioid receptor antagonist)	Opiate overdose Opioid-induced postoperative respiratory depression (0.1-0.4mg IV)	Improves blood flow in experimental spinal contusion (the effect is prevented by vagotomy or atropine) [10 mg/kg] Improves neurological recovery after experimental spinal injury (2 mg/kg/h) Reverses hypotension after experimental concussive brain injury (10 mg/kg) Reduces neurological deficits after acute ischaemia in primates and cats (2-7 mg/kg) Transiently reverses ischaemic neurological deficits in man (0.4mg IV; for references see review by McNicholas & Martin 1984) Acute spinal cord injury (clinical trial in progress; Flamm et al. 1985)

Table X. Major findings of studies reporting infectious disease morbidity and mortality patterns in intensive care unit (ICU) patients

Reference	Setting	Results
Daschner et al. (1982)	General ICU	Infection control programme, nurse epidemiologists and subrapubic bladder drainage improved infection rate
Goldmann et al. (1981)	Neonatal ICU	Staffing and environment play critical role
Machiedo et al. (1981)	Surgical ICU	Research needed to explore cellular mechanisms likely to be the key of sepsis-related organ failure
Caplan & Hoyt (1981)	Trauma unit	Doubtful role of antibiotics, which should be used as late as possible
Allgöwer et al. (1980)	Surgical ICU	Priority given to early and aggressive treatment of respiratory and circulatory failure
Meakins et al. (1980)	Surgical ICU	Critical role of definitive surgery, immunological defence, adequate nutritional support
Stevens et al. (1974)	Respiratory ICU	Various systemic antibiotic regimens did not increase survival in acquired pneumonia; ?polymyxin aerosol in prophylaxis
Hemmer & Hemmer (1981)	Surgical ICU	Survival improved after proper antibiotic treatment (retrospective study)
Pottecher et al. (1979)	Surgical ICU	Doubtful efficacy even of appropriate pharmacological intervention
Langer (unpublished, 1979)	General ICU	Antibiotic drug efficacy in about 45% of cases; mainly minor complications

of the setting in improving the infection rate and severity has little to say for antibiotics (Goldman et al. 1981). On the other hand, the two more drug-oriented studies (Pottecher et al. 1979; Stevens et al. 1974) which failed to provide evidence of a positive role of antibiotics in improving survival and decreasing the spread of infections must be criticised for their poor clinical pharmacological approach, which could have been one of the reasons for their 'negative' results.

Surgical drainage and eradication of the focus is obviously the single most important and effective step in the treatment of infection (Meakins et al. 1980; Rapin & George 1983). Hence, the major challenge for antimicrobial treatment comes from infections such as pneumonia, bacteraemia or meningitis which are not amenable to surgical intervention. The state of the art in this field can be summarised in 6 points, which also provide a possible framework for the urgent, but difficult task of producing reliable data.

1. The host-environment relationship where a pharmacological anti-infective measure is taken is the most decisive factor in determining the overall outcome. Table XI provides a problem-oriented guide to the major risk factors, which must be considered critical variables when instituting and evaluating prophylactic and/or therapeutic treatment.

2. The pathogenetic potential of an intensive care unit environment – where invasive procedures and the risk of cross-infection are associated with the high vulnerability of the critically ill patient – should be combated with careful preventive measures. The well-documented, mandatory preventive measures shown in table XII are largely the same as the various recommendations based on clinical common sense, and do not provide a ready-to-use solution (Eickhoff 1981).

3. Clinical pharmacology is often held up as important in setting optimum guidelines for therapeutic schemes. Such confidence is based on an expected ability to describe and predict the pharmacokinetic behaviour of various drugs which are handled in the body by organs whose function is often rapidly changing, and which have to find their way into tissues and organ 'sanctuaries' where the infecting organisms exert their effect and multiply. Standard pharmacokinetic guidelines and monitoring of serum concentrations (and in selected cases, of other tissues or biological fluids) must be

Table XI. A problem-oriented guide to mapping of the risk of ICU-acquired infections

1. ICU environment		
Source of infection	Transmission	Clinical importance in the ICU
Inanimate environment	Airborne route	Minor (except for humidifiers and air-conditioning apparatus; may also be important for virus infections, *Staphylococcus aureus* infections, tuberculosis, and in burns units)
Infected patients	Contact (hand, instruments)	Major
Autogenous flora	Breakdown of host defence	Major
2. ICU host		
Risk factors	Mechanisms	Clinical importance in the ICU
Breakdown of:		
physical barriers	As a consequence of illness	Major
	As a consequence of treatment	Major
immunological defences	Pre-existent	
	Trauma-induced	Entity not well established
	Pharmacological treatment	
3. Micro-organisms[a]	Most relevant role in	Comments
Aerobes		
Gram-positive	Wound, skin, soft tissue infections; bacteraemias (≈ 20-30%); lower respiratory tract infections < 20%	Human reservoirs important in wound and soft tissue epidemics. Airborne route possible (burns units) for *Staphylococcus aureus*
Gram-negative	ICU-acquired infections (≈ 70%); urinary tract infections; late-onset pneumonia, bacteraemias, intra-abdominal infections; neonatal meningitis	Gram-negative colonisation of skin, oropharynx and respiratory tract occurs early in the critically ill
Anaerobes	Intra-abdominal and pelvic infections; early-onset pneumonia (aspiration); empyema; wound infections	Patients' autogenous flora is the only important reservoir (except for clostridial wound infection)
Fungi (mainly *Candida*)	Colonisation of GI tract; lower respiratory tract infections and sepsis; endophthalmitis	Association with long term use of broad spectrum antibiotics and/or total parenteral nutrition
Viruses	Lower respiratory tract, CNS and systemic infections in the compromised host	Information is scarce and poorly documented

a The environment, the staff, and patients should be considered routine 'hosts' of concentrations of micro-organisms which may vary (according mainly to crowding and ventilation conditions). A positive finding for bacterial presence should be considered clinically relevant *per se* only if it refers to specific sites, such as the blood and CSF. The pathogenic potential of other colonisations should be evaluated in each case, taking into account the overall clinical picture. The epidemiology of the patterns and trends, bacterial selection, resistance and transfer of resistance must be considered an ecological hospital- and ICU-specific problem.

Table XII. Mandatory, well-documented preventive measures for minimising the risk of cross-infection in the ICU and minimising the risk of infection in individual patients

Environment-oriented measures (to minimise the risk of cross-infection)
• appropriate space and trained personnel
• aseptic invasive manoeuvres
• sterilisation and disinfection of devices and apparatus
• hand washing
• [isolation measures]
Patient-oriented measures (to minimise the risk to individual patients and enhance defence mechanisms)[a]
• definitive surgical treatment
• shortest possible permanence of invasive devices
• restriction of immunosuppressive treatments
• [antibiotic prophylaxis]

a Active 'immunomodulatory' pharmacological treatments have by no means been proven useful, with the obvious, rare exception of clinical conditions which require 'substitutive' intervention for documented immunodeficiencies.

applied in cases of organ failure (Bennet et al. 1977). The expectation is fully justified, but for the time being it still needs confirmation in routine clinical settings.

4. Clinical microbiology may play a more important role than clinical pharmacology. Virtually all micro-organisms have been found to be potential pathogens in the critically ill and any tentative ranking of their importance may be misleading. The clinical condition, the setting, and the problems of bacterial selection, emergence of resistant strains, transfer of resistance and transfer of resistant strains require comprehensive, attentive surveillance to detect the agent responsible in good time. Clinical microbiology specific to the intensive care situation is faced with apparently insurmountable obstacles, judging from the scant available information. Clinical experience tends to bear out this unsatisfactory state of affairs, because of the objective difficulties in distinguishing harmless colonisation from harmful infection, the incompatibility between the urgency of clinical questions and the time microbiologists need to find relevant answers, and the sophistication required to sample and grow representative and reliable specimens – which is complicated even further by the presence of mixed infections.

5. Prophylaxis, the classical controversy of antibiotic usage (short of hard specific data for most intensive care conditions), must be based on the principles accepted in other areas of medicine: short term perievent treatment with the narrowest spectrum agents should be the rule. Only experimental data suggest the usefulness of prophylaxis even some hours after contamination (Miller & North 1981).

6. Life-threatening conditions, where very active and timely anti-infective treatment could be crucial, have to be faced, *de facto*, on mainly empirical grounds. The recommendations in table XIII summarise current knowledge with respect to how a specific condition of the host can most appropriately be treated.

Table XIII. Emergency treatment for sepsis

Clinical setting	Treatment
Previously healthy/community-acquired[a]	
Aerobes (Gram positive/ Gram negative) suspected	Penicillinase-resistant penicillins Aminoglycosides or 'third generation' cephalosporin
Aerobes and anaerobes suspected	Aminoglycosides or 'third generation' cephalosporin Penicillin G in high dosage Clindamycin or metronidazole or chloramphenicol
Immunocompromised and/or hospital-acquired (life-threatening)[b]	
Gram negative aerobes, *S. aureus*, fungi, resistant strains suspected	Amikacin or 'third generation' cephalosporin or azlo-, mezlo- or piperacillin (± vancomycin) Antimycotic treatment

a Treatment is not adequate for infections due to mycobacteria, fungi, Mycoplasma, or *Legionella* sp. and similar causal agents of interstitial pneumonia. Resistant strains must be considered (e.g. *Pseudomonas* sp., *S. aureus*).

b Treatment is not adequate or optimal for infections due to Gram-positive aerobes, some anaerobes, mycobacteria, *Pneumocystis carinii*, or Mycoplasma.

3.3 Cardiovascular Emergencies

The three main variables which interplay in determining the dynamic, partially self-regulating, circulatory status are: (1) the circulating volume; (2) cardiac function; and (3) extension of the vascular bed, which in intensive care patients may be specifically affected by any of the most frequently occurring critical conditions listed in table XIV. The type and the priority of the various forms of pharmacological and non-pharmacological treatments should be evaluated against this background. A few general principles are worth emphasising before focusing on specific measures:

1. Complex and multiple interactions are the rule in cardiovascular emergencies arising in the intensive care unit. The rationality of the therapeutic approach depends directly on the degree of accuracy achieved in ranking and correlating the variables to be taken into account.
2. Rapid, spontaneous modifications of the haemodynamic status call for particular caution in passing a positive or negative judgement on any one pharmacological treatment. A conservative attitude is mandatory when no carefully controlled comparative data are available to support the role of new drugs or treatments.
3. An intelligent surveillance strategy may be more useful and informative than active intervention. Intrinsic compensatory circulatory adjustments, though abnormal (e.g. tachycardia in hypovolaemia or hyperthermia) may be satisfactory and in fact better tolerated in certain clinical situations than prompt 'normalisation'.
4. Adequate tissue perfusion (when organ function is threatened) and circulatory stability (when compensatory mechanisms are at risk of breakdown) are the key terms of reference for any intervention strategy.

The most common situations requiring prompt ad-

Table XIV. Clinical and pathophysiological situations frequently seen in the intensive care unit leading to impairment of cardiovascular function

Cardiovascular function affected	Clinical situations	Priority in therapeutics
Circulating volume (reduced)	Haemorrhage	Fluid replacement
	Sepsis	
	Burns	
	Postoperative period	
	Intestinal occlusion	
	Multiple trauma	
Cardiac function		
Contractility	Toxic concentrations of some drugs (barbiturates, phenothiazines, calcium antagonists, β-blockers, tricyclic antidepressants)	Remove the causative factors Correct the altered biochemical variables
	Prolonged anaesthesia (halothane)	Use inotropic agents as temporary support
	Hypothermia, acidosis, severe hypoxaemia	
Mechanics	Myocardial contusion and/or infarction	Reduce left ventricular load
	Cardiac tamponade	Remove blood or fluid from pericardium
	Biventricular dysfunction (pulmonary embolism, severe respiratory insufficiency, PEEP)	Reduce mechanical overload
Electrics	Severe rhythm disturbances	Correct causative factors
Vascular bed		
Reduced	Severe vasoconstriction (fluid loss, enhanced catecholamine drive)	Vasodilating (α-blocking) agents with fluid replacement
Augmented	Hyperdynamic states (sepsis)	Adequate fluid replacement
	Lack of vasomotor tone (spinal cord injury, pharmacological substances)	Temporary vasopressor agents

justment are those involving imbalance between the circulating volume and the size of the vascular bed, with impending or actual circulatory failure.

3.3.1 Fluid Replacement Therapy

Adequate fluid replacement is of prime importance in all cases in which intravascular volume is reduced. It is important that fluid replacement be 'adequate', not merely 'normal', in order to correct a pathological circulatory pattern. For example, in a situation of generalised loss of vasomotor tone (see table XIV) fluid replacement must be higher than normal, until physiological or pharmacological measures reduce the abnormal extension of the vascular bed.

3.3.2 Drugs Which Modify Peripheral Vascular Resistance

Vasoactive drugs are important adjuvants to fluid therapy, as they help to restore and maintain a stable haemodynamic setting by modifying the extension of the vascular bed. Their rational use depends on the accuracy of information available on circulatory patterns and on timely monitoring of the patient's clinical conditions. The main intensive care conditions where these drugs are used are:

1. During volume replacement, to maintain adequate perfusion pressure to vital organs as long as necessary
2. In patients with poor cardiopulmonary function, where rapid volume loading could be harmful
3. In prolonged depression of vascular tone with abnormal expansion of the vascular bed requiring sustained fluid replacement to prevent excessive loss of water into the extravascular space
4. In some stages of septic shock with very low peripheral vascular resistances, to restore the normal extension of the vascular bed
5. For dopamine alone, at very low doses (dopaminergic effect) to improve renal blood flow in renal insufficiency due to circulatory failure.

3.3.3 Inotropic Agents

Primary pump failure is a very rare event in patients admitted to a general intensive care unit. Most often, multiple factors lead to *secondary* depression of cardiovascular function (see table XIV). In most instances cardiac failure is seen as the final stage of multisystem organ failure.

A rational therapeutic approach must be to remove, or treat, the aetiological factors; a vasoactive drug with inotropic properties should be considered only as a temporary support for the vascular system until it is completely stabilised. Inotropic agents are often administered in clinical conditions (e.g. the postoperative period, pulmonary embolism, respiratory insufficiency, mechanical ventilation with PEEP) which do not represent specific indications, and where the efficacy of drug treatment has not been confirmed in properly conducted clinical trials (see also below).

Digitalis is best avoided (Herbert & Tinker 1980) because of its weak inotropic action and because in the many abnormal pathophysiological situations encountered in patients in the intensive care unit, its pharmacological action may be altered, with a resultant increased incidence of toxic effects (Opie 1980). In rare conditions when myocardial contractility is selectively depressed (e.g. in drug intoxication; see table XIV), dobutamine, glucagon or isoprenaline (isoproterenol) are preferred, provided no associated severe arrhythmia is responsible for the vascular failure.

3.3.4 Antiarrhythmic Drugs

Table XV shows the most common conditions which can be associated with cardiac rhythm disturbances in general intensive care patients. With the obvious exception of life-threatening arrhythmias, general supportive measures of intensive care, without specific drug treatment, provide a satisfactory solution. Antiarrhythmic therapy is a matter of clinical judgement, and should be based on aetiological factors, the background of a particular illness, and the patient's haemodynamic balance. To avoid inappropriate or unjustified use of drugs, priority should always be given to removing all possible causes of arrhythmias. This is best illustrated with three examples:

1. *Arrhythmias due mainly to abnormalities in the ventilatory pattern:* normalisation of ventilation

Table XV. Most common causes of arrhythmias in general intensive care patients

Disturbances of basic physiological variables
• hypoxia/hypercapnia
• metabolic alkalosis/acidosis
• hypokalaemia/hyperkalaemia
• hypercalcaemia
• anaesthetic agents (especially inhalational anaesthetics)
Pharmacological causes
• muscle relaxants (especially depolarising agents)
• intoxication from: antiarrhythmic drugs, phenothiazines, tricyclic antidepressants, digitalis
Clinical situations
• pain (postoperative, trauma)
• cerebral accidents
• pulmonary embolism
• sepsis
• respiratory insufficiency, ARDS
• some forms of tetanus
• spinal cord injury
• intracardiac devices (temporary pacemakers, monitoring catheters, central infusion line)

and the blood gas picture usually reverses the arrhythmias (Ayres & Grace 1969).

2. *Arrhythmias due to major respiratory or vascular impairment (ARDS, pulmonary embolism, sepsis), most of which are supraventricular in origin:* the severity of the underlying disease is a challenge to the clinician, and any antiarrhythmic treatment, though temporarily beneficial, ultimately fails. When the basic process has a favourable course, an attempt to avoid circulatory breakdown is justified. Intravenous amiodarone, verapamil or β-blockers are the drugs of choice.
3. *Arrhythmias due to drug intoxication:* the rule here is to avoid drug interactions with their unpredictable effects. The basic property is to remove the exogenous substance(s) entirely, if possible, and to monitor closely the patient's ECG. Obviously, all abnormalities in serum electrolytes and gas exchange should be corrected. Life-threatening arrhythmias – such as extreme bradycardia, sinoatrial or atrioventricular block, or 'torsade de pointes' – are best treated by a temporary pacemaker.

3.3.5 Treatment of Pulmonary Embolism

The basic pathophysiological condition in pulmonary embolism is a mechanical impairment of the right ventricle outflow, with pressure overload on the same chamber. The dilated right ventricle reduces left ventricular compliance and the diastolic filling volume (McIntyre & Sasahara 1974). The more severe the pulmonary obstruction, the less is the left ventricle inflow, which leads to a low cardiac output and shock. Because cardiac contractility is not impaired, there is no rationale for inotropic drugs *per se,* but if shock is present, vasoactive drugs should be considered to sustain blood pressure and to assure blood flow to vital organs. Efforts should be focused on reducing the degree of obstruction in the pulmonary circulation.

3.3.6 Management of Shock

Adequate tissue perfusion and duration of shock are the main factors which influence survival (Weil & Nishijima 1978). The immediate replacement of lost fluid therefore has priority. Low cardiac output with adequate filling pressure is usually observed in the late stages of multisystem organ failure. Although inotropic agents are generally used, their long term efficacy is not proven and the prognosis depends mainly on whether prolonged damage to vital organs has occurred.

3.3.7 Management of ARDS

In recent years, many studies have demonstrated the pathological consequences of mechanical ventilation with PEEP on the circulation. In ARDS, both PEEP and right ventricular stress markedly alter the interventricular relationship, leading in the most severe cases to 'left ventricle tamponade' and a fall in cardiac output (Laver et al. 1979). As in major pulmonary embolism, the low output is due to mechanical abnormalities and does not itself require inotropic support. However, vasopressive agents are widely used to sustain blood pressure and counteract the negative haemodynamic effect of PEEP (Hemmer & Suter 1979).

The use of vasodilators (such as sodium nitroprusside) to 'unload' the right ventricle (Petty & Fowler 1982), though theoretically acceptable, can-

not claim reliable data confirming its lasting efficacy. In the late stages of ARDS, severe anatomical damage in the pulmonary circulation dictates the poor prognosis, and vasoactive or inotropic agents are unlikely to improve the outcome (Pontoppidan & Rie 1982).

3.4 Problems of Haemostasis

The control of haemostasis processes, either in terms of prophylaxis or treatment with drugs or blood components, is in the forefront of the clinical concerns in the intensive care unit setting, mainly for two types of patients: (a) those admitted for specific and severe haemostatic (haemorrhagic or thrombotic) problems; and (b) those who present with pathologies at high risk of haemostatic complications.

Two key drug groups, anticoagulants and fibrinolytic agents, are most often used. Antifibrinolytic drugs are very rarely indicated or needed, and will not be discussed here. Because they are still advocated and used, it is worth stressing that the so-called 'haemostatic drugs' should be left out of any therapeutic or prophylactic armamentarium, as they lack any theoretical or clinical foundation (Verstraete & Vermylen 1982).

A common problem lies in the use of blood components, whose main clinical application is in massive blood loss. This is a frequent event in intensive care practice which besides being life-threatening *per se* may be associated or followed by haemostatic failure through any combination of the events or factors listed in figure 3.

3.4.1 Management of Massive Blood Loss

The risk of a situation changing from one of

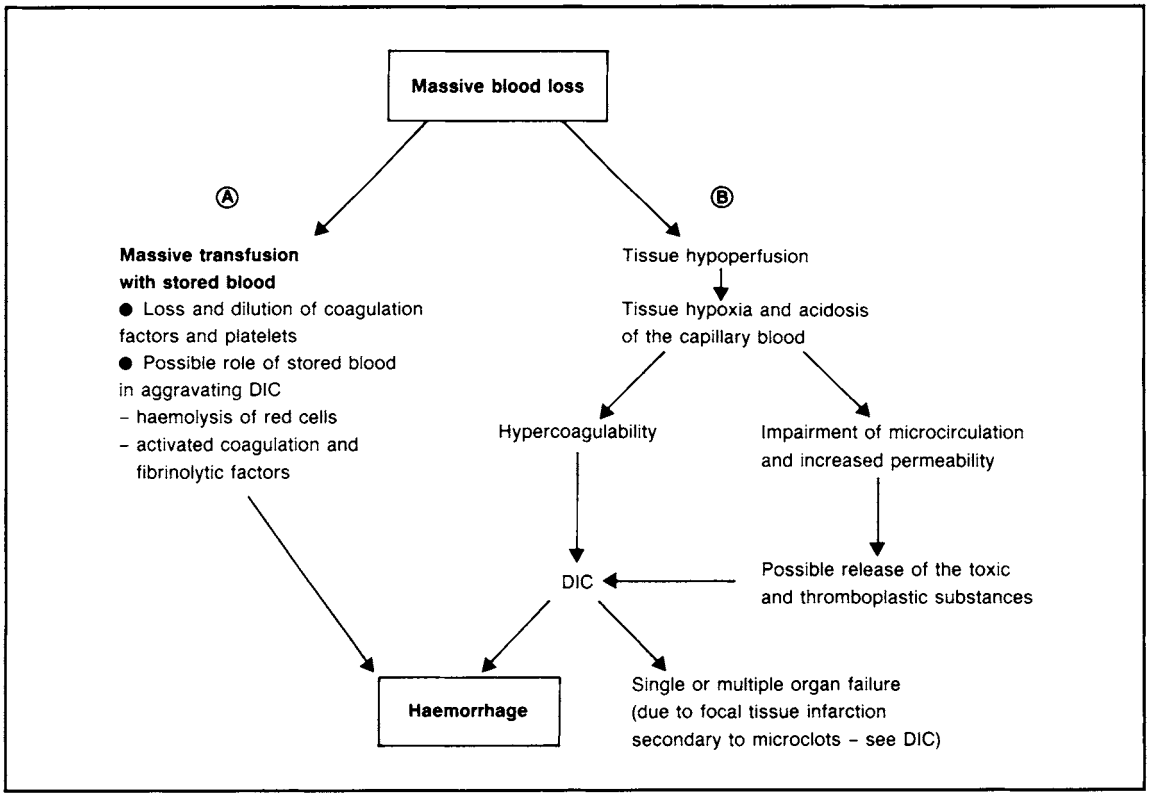

Fig. 3. Possible factors leading to haemostatic failure following massive blood loss or transfusion (DIC = disseminated intravascular coagulation).

Table XVI. End-points of management of massive blood loss

Aims	Interventions
1. To assure adequate cardiac output	Volume replacement colloids/crystalloids blood inotropic agents
2. To assure adequate O_2 transport	Blood whole packed red cells
3. To prevent and/or treat haemostasis imbalance	Blood components replacement fresh frozen plasma platelets (blood warm and not anticoagulated)
4. To prevent and/or treat multisystem failure	1 + 2 + 3 + adequate patient monitoring

massive blood loss to one of haemorrhage must be met: (a) through comprehensive clinical surveillance of sequence B in figure 3 (whose evolution is mainly dependent on the underlying pathology); and (b) through the rational use of a transfusion strategy.

The key elements of clinical management of massive blood loss are summarised in table XVI, which is also a reminder of the corresponding discussion in section 3.3 (with respect to circulating volume and cardiac output). Stored whole blood is still widely considered to be the only readily available form of red cells and volume (and for this reason it is shown alone in figure 3), the only caveat to this being that when storage is longer than 24 hours it contains non-functioning platelets, and no more than 10% of factor V or 20% of factor VIII (Benson & Isbister 1980). Fresh frozen plasma contains the natural inhibitors of coagulation and fibrinolysis (antithrombin-III and antiplasmin) as well as the coagulation factors. It therefore has the capacity of reducing the loss and dilution of coagulation factors, and of preventing or correcting possible disseminated intravascular coagulation (DIC) with its sequelae of multiple organ failure.

The role of fresh blood is still controversial (Counts et al. 1979; Loong et al. 1981) with respect to its definition (blood stored for less than 24 hours, or warm blood which is not anticoagulated). The few cases who have responded only to blood obtained by direct transfusion, after all haemostatic factors have been corrected, suggest that unknown factors of haemostasis are transfused with fresh warm non-anticoagulated blood (Editorial 1976; Sheldon & Blaisdell 1975). Because of the inherent risk of any direct transfusion, this practice should be reserved for the very rare 'resistant' cases and evaluated with *ad hoc* research protocols.

3.4.2 Management of Disseminated Intravascular Coagulation (DIC)

Disseminated intravascular coagulation can be seen as an intermediary disease mechanism, which can occur in a variety of clinical conditions, where blood coagulation is triggered by one of the factors shown in figure 4. This results in fibrin deposition in the microcirculation with subsequent organ failure.

Haemorrhage may appear when the consumption of platelets and/or coagulation factors exceeds the rate of synthesis (Mant & King 1979; Preston 1982). The rationale for any intervention strategy is to address simultaneously various goals which can be ranked as follows (Verstraete & Vermylen 1982):

1. Assure adequate tissue perfusion and oxygenation
2. Remove the triggering cause, if known and accessible
3. Break the chain of events shown in figure 4
4. Replace deficient factors.

Guidelines for the first two goals (1 and 2) are covered by standard principles of treatment of multiple organ failure, of ablative surgery (e.g. in case of septic abortion or tumour masses), and of general pharmacological intervention (e.g. for sepsis or eclampsia). For the purposes of this discussion, the latter two goals (3 and 4) merit specific attention as being those where specific pharmacological treatment may play a role. The scant information available can be summarised as follows:

1. The efficacy of *heparin* in positively influencing the morbidity and mortality associated with dis-

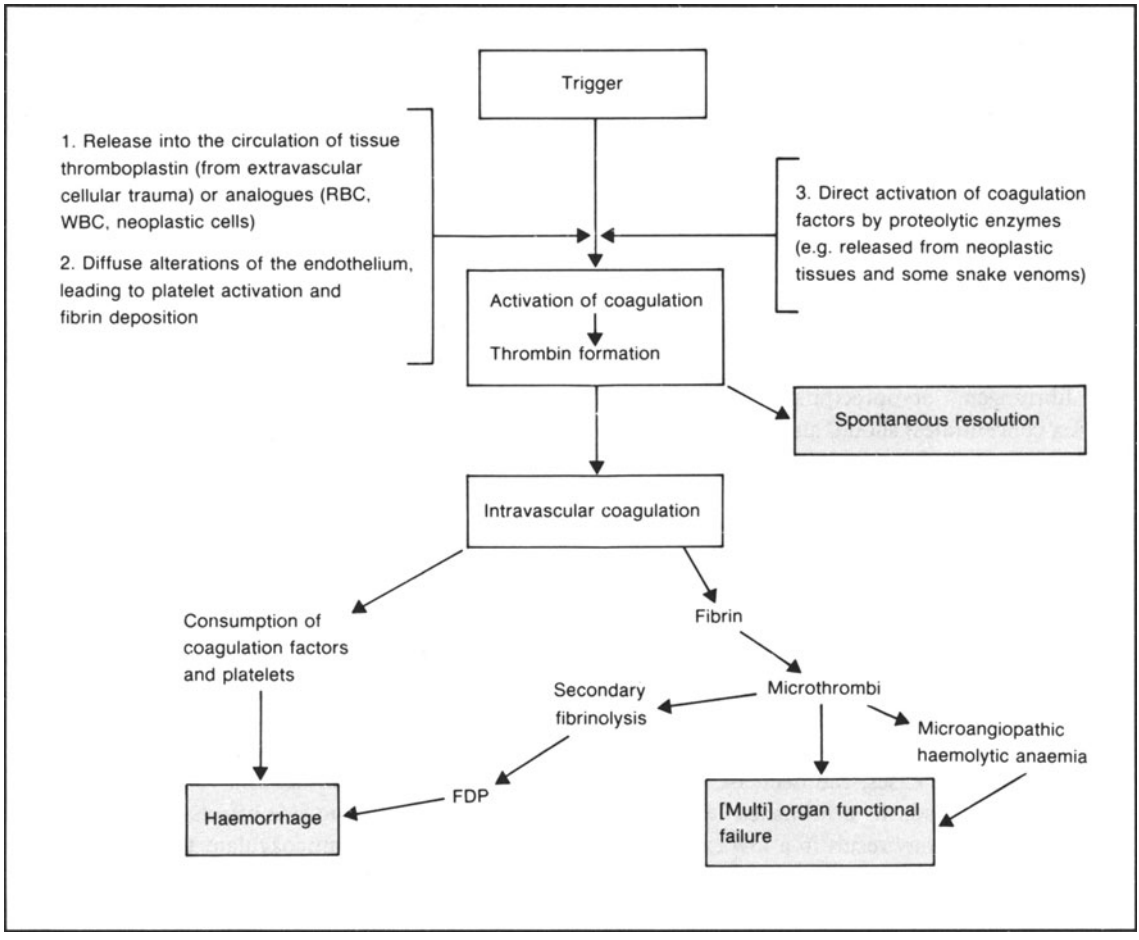

Fig. 4. The sequence and interplay of factors and events involved in leading to and derived from coagulation problems (FDP = fibrin degradation products; RBC = red blood cells; WBC = white blood cells).

seminated intravascular coagulation is far from proved. A *possible* role is seen:

(a) in some cancer patients;

(b) in obstetric situations (once the intrauterine cause is removed);

(c) as a third-line drug, when plasma plus anti-platelet drugs and plasmapheresis have failed and;

(d) in thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome. As a general rule, heparin should be reserved for severe haemorrhagic complications and/or vascular thrombosis, with or after the administration of blood components.

2. When replacement of deficient (consumed) factors is needed, fresh frozen plasma is the first-line treatment, as in more complex conditions than a simple lack of fibrinogen, it provides the natural inhibitors of coagulation and fibrinolysis, antithrombin-III and antiplasmin, as well as coagulation factors. It also serves as a plasma expander.
3. Platelet concentrates may be useful when the platelet count is $\leq$ 30-50,000/μl and consumption has not stopped.

4. Data on antithrombin-III (which may block intravascular coagulation without affecting local haemostatic processes; Liebman et al. 1983) are presently too scanty, and restricted to patients with severe hepatic failure, to permit the formulation of precise guidelines for its use.

Antifibrinolytic drugs are contraindicated, as it is irrational to try to stop a *natural* defence mechanism against vascular occlusion. Moreover, a definite risk of aggravation of the patient's condition may follow, such as the evolution of haematuria into anuria. Concentrates of blood clotting factors (e.g. fibrinogen, cryoprecipitates, prothrombin complex concentrates) should also be avoided since they may contain activated clotting factors and therefore may aggravate the progression of disseminated intravascular coagulation.

3.4.3 Management of Pulmonary Thromboembolism

Pulmonary emboli result in partial or total occlusion of the vascular bed. The basic pathogenetic feature is a mechanical obstacle to pulmonary blood flow, causing a higher right ventricular workload. In the most severe cases, the decrease in pulmonary blood flow leads to diminished left ventricular filling, which may result in a low cardiac output and shock. Clinically, this translates into only a minority of patients (27%) surviving the first hour after the event (Bell & Simon 1982) and in whom management can be offered (as outlined in table XVII). Possibly also because of the difficulties inherent in a satisfactory standardisation of the diagnosis, the very few properly controlled trials that have been conducted have been in small and largely non-comparable populations (Ly et al. 1978; Tibbutt et al. 1974; UPET 1973), and their results may be seen at best as a contribution to serendipidous guidelines:

1. Thrombolytic therapy [streptokinase, urokinase, or one of the newer agents such as tissue-type plasminogen activator (Collen 1983) which have been tested up until now mostly in coronary conditions] is the first choice when the haemodynamic impairment requires rapid removal of the obstacle from the pulmonary vascular bed.

Table XVII. Management of major and massive pulmonary embolism

Objectives	Management
Diagnosis not established	
To maintain essential bodily function:	
combat hypoxia	O_2
support of the circulatory system and pulmonary blood flow	Adequate fluid therapy Standard cardiovascular treatment
prevent additional accretion of thrombus	Heparin
Diagnosis established	
To remove the obstacles	Thrombolysis Embolectomy
To maintain circulatory function	Standard cardiovascular treatment
To prevent further emboli	Heparin Oral anticoagulants Vena cava interruption

2. Anticoagulant therapy has been included in clinical trials as a mandatory follow-up for maintenance of the thrombolytic effect and must be seen as a key component of management aiming at the prevention of further emboli.

3. Haemorrhagic side effects may follow both thrombolytic and anticoagulant therapy. The true incidence is unknown, as the rates reported in randomised clinical trials derive from unusually well controlled and selected patients. It is worth stressing that heparin (Porter & Jick 1977) is no less, and possibly even more likely to cause haemorrhagic side effects than thrombolytic agents. The bleeding which may follow administration of thrombolytic drugs is mostly a direct result of the invasive procedures needed to follow the evolution of the thrombotic process and the haemodynamic setting.

4. Surgery for embolectomy is the exception (mortality is still unacceptably high) and must be considered only when cardiac arrest follows or is associated with massive pulmonary embolism, or in the presence of absolute contraindications to anticoagulant and thrombolytic drugs in haemodynamically compromised patients. Vena caval interruption should be reserved for patients in whom

anticoagulation is absolutely contraindicated (or anticoagulant and/or thrombolytic therapy has failed) *and* a further embolus would be life-threatening (Bell 1982).

3.4.4 Prevention of Pulmonary Embolism in Severe Trauma

Prevention of pulmonary embolism in severely traumatised patients is of specific interest since:

1. Severely traumatised patients are at high risk of thrombotic complications (Coon 1977). This is due to severe tissue damage and subsequent blood clotting activation, coupled with other risk factors (e.g. immobilisation, possible negative water balance, possible surgical intervention).
2. Severely traumatised patients may be or are at risk of haemorrhage. Even minor bleeding may be very serious when localised in particular regions (e.g. the brain, pericardium, spinal cord).
3. Practically no information has been obtained directly in this group of patients. 'One must decide on an approach to prophylaxis by extrapolation from studies of other conditions, a perilous undertaking' (Salzman & Davies 1980).

The last caveat is even more challenging, and worrying, when the currently used prophylactic treatments are considered (Salzman & Davies 1980). Oral anticoagulants fare better than other treatments (though their benefit has not been proven in terms of mortality reduction, possibly because of the small size of the tested populations), but carry the highest risk of severe haemorrhagic complications. This calls for the closest monitoring of laboratory variables to avoid mainly too low, and therefore ineffective, dosages. These drugs are further seen as controversial in orthopaedic and trauma patients and cannot be used in such clinically important categories as patients with head, pericardial, retroperitoneal or medullar trauma.

A rationale for *low dose heparin* (whose value has been proven in cases of elective surgery) does not exist, since significant amounts of circulating activated blood clotting factors are present when the patient comes to medical or surgical attention (Blaisdell 1979). *Dextrans*, which do not require laboratory monitoring, could be a useful choice, but available data (referring to populations treated with two different molecular weight molecules) do not provide any consistent guidelines with respect to efficacy, dosage or duration of treatment (Bell 1982). While the risk of allergic reactions can be definitely considered low, haemorrhagic complications and the risk of fluid overload could become clinically relevant. Other procedures including 'physical' manipulation (physiotherapy, muscular electrostimulation, etc.) have been tested in non-traumatised, very low-risk patients.

4. Conclusions

Clinical conditions encountered in general intensive care units represent a uniquely challenging situation for what should be considered a common goal of clinicians and clinical pharmacologists: the application of scientifically sound criteria to the routine care of patients and, at the same time, to the development of new knowledge on the many unanswered questions concerning overall management and the use of specific drugs and treatment strategies. Our collaborative analysis of the published literature and of the approaches adopted in the various settings has underlined the basis from which this review originated: there is an urgent need for studies which allow the evaluation of individual treatments in the broader context of overall care. The philosophy and the sequence which have been adopted for the presentation and discussion of the various critical care situations seem to offer a good basis for revising practices used in different centres, and for defining the problems to be considered when planning prospective or retrospective controlled therapeutic or prophylactic interventions.

The traditional core of clinical pharmacology, clinical pharmacokinetics, should be seen: (a) as a very simple series of descriptive data sets on the pharmacokinetic behaviour of single compounds, which should be made available to clinicians working with intensive care patients, mainly to avoid drug-related side effects and in certain specific cases (e.g. the use of barbiturates) to allow a better control of the treated problems; and (b) as a conceptual basis for understanding and investigating,

through monitoring of the pharmacokinetic behaviour of drugs, the modification of physiological compartments and functions.

The interplay and the interdependence of the main background conditions which are found in critically ill patients (altered nutritional status, fluid balance and respiratory function) with specific organ-related problems appear to have been up until now scarcely investigated. In this respect, it is interesting to note that the clinical syndrome ARDS may be described and approached differently depending on the expertise of the clinician in charge of the affected patient (Editorial 1986). In this review an attempt has been made, within the individual areas, to identify a logically common strategy where the order of priorities is stressed, and where drugs may be clearly appreciated as a dependent variable.

The particularly complex situations which are the rule in general intensive care settings have so far favoured studies based on single-centre protocols, where standardised conditions of observation and treatment are assumed to be more easily assured. The advantage of this approach is obvious with respect to standardisation. However, the adoption of multicentre protocol designs for experimental and controlled evaluations of the outcome of different routine management strategies seems to be a worthwhile alternative to allow for the assessment of therapeutic and prophylactic interventions on larger populations. Appropriate stratifications could then offer new opportunities for understanding the role of the many variables which determine the final outcome of the various subgroups of patients.

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