Novel Monoclonal Antiendotoxin Antibody Therapy
Efficacy at Any Price?

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The United States spends in excess of $US2 billion each day for healthcare. This expenditure, approaching 12% of the Gross National Product, represents the largest per capita healthcare cost in the world. The future direction of healthcare in the US, and mechanisms for providing universal healthcare coverage, were debated in the recent current presidential election (Angell 1992; Clinton 1992; Enthoven 1992; Reinhardt 1992; Sullivan 1992). In the absence of a national plan for defining and distributing healthcare resources, the cost of healthcare has exceeded the rate of inflation for a number of years. The conflict between our desire for the latest technology or drug therapy to treat specific diseases, and our unwillingness or inability to pay for such therapy, will not be resolved in the immediate future (Coile 1990). In the absence of consensus regarding funding priorities, the decision to use or not to use a new therapy is made at the patient’s bedside. This is in contrast to national healthcare programmes available in some European countries and Canada.

The effect of new technologies on healthcare costs and on the nation’s ‘health’ was recently discussed (Massaro 1990). Since unlimited funding does not ensure maximal therapeutic outcome, an appropriate balance between the cost of therapy and the maximum treatment benefit achieved must be obtained to ensure cost-effective healthcare. Recently, several publications have reviewed the principles of cost effectiveness as well as the cost effectiveness of accepted interventions (Chatterjee & Srebro 1990; Detsky & Naglie 1992; Freund & Dittus 1992; Hurley 1990; Puma & Lawlor 1990; Schulman et al. 1991; Smith 1990). In at least one publication, the increase in healthcare costs, associated with the introduction of new technology, has not resulted in improvements in patient outcome (Shy et al. 1990). Although complete information regarding the benefits and costs of new therapies should be provided to the clinician prior to their introduction, the majority of clinical trials provide little information to the clinician about mechanisms for integrating the results of the trial into patient care policies (Hawkins 1984).

The development of monoclonal antiendotoxin antibodies for the treatment of serious Gram-negative infections has initiated considerable debate regarding the appropriate use of high-cost pharmaceutical products (Greenman et al. 1991, 1992; McCabe 1992; Spalter 1992; van Deventer 1992; Warren et al. 1992; Wenzel 1992; Ziegler & Smith 1992; Ziegler et al. 1991a,b). Prior to the introduction of these products, most new drug products were replacements for existing therapy and were often associated with only minimal increases in treatment costs. The advantages of the new products, including improved tolerability profiles or better patient compliance, were used by pharmaceutical companies to justify their increased costs. The antiendotoxin antibodies represent a new group of products that have the potential to alter disease processes without offering substantial cost savings.
More importantly, they will not replace standard drug therapy.

Schulman and colleagues have estimated that the total increase in health costs associated with the use of antiendotoxin antibodies may exceed $US2.3 billion ($US1.5 billion in drug costs) with strict guidelines for use, and could exceed $US6.2 billion if their use is unrestricted (Schulman et al. 1991). Although cost has not been the major focus of recent letters and editorials, the efficacy of these agents has been scrutinised in leading medical journals (Greenman & Schein 1992; Greenman et al. 1991; McCabe 1992; van Deventer 1992; Warren et al. 1992; Wenzel 1992; Ziegler & Smith 1992; Ziegler et al. 1991a,b).

This article reviews the processes traditionally used in the US for evaluating new drug therapies, and mechanisms for controlling their use into clinical practice. It also attempts to point out limitations that may apply to the evaluation of these new agents, and it concludes with recommendations for future evaluation of the cost effectiveness of new products.

1. Monoclonal Antiendotoxin Antibodies and Sepsis

The monoclonal antiendotoxin antibodies have recently been evaluated for the treatment of patients with serious Gram-negative infections (Greenman et al. 1991; Ziegler et al. 1991a). The organisms most commonly associated with these infections contain a lipopolysaccharide (endotoxin) component in their cell wall which has been associated with the adverse systemic reactions seen in these patients. This syndrome is commonly referred to as the sepsis syndrome and when it occurs in the presence of hypotension is called septic shock (Parrillo et al. 1990). The systemic response to endotoxin release may result in hypoperfusion and/or dysfunction of major organ systems including the lung, kidney, heart, liver and brain (Bone et al. 1989). The mortality of patients with sepsis syndrome approaches 50%, despite the introduction of antibiotic therapy and cardiovascular support (Parrillo et al. 1990). Unfortunately, prospective criteria for the diagnosis of sepsis do not adequately identify those patients likely to develop sepsis, septic shock or their associated morbidity. In addition, patients with Gram-positive infections may develop sepsis and septic shock, and are unlikely to respond to antiendotoxin antibodies. Although endotoxin has been strongly associated with the development of sepsis, a number of other mediators of the sepsis syndrome have also been identified (Parrillo et al. 1990). A complete description of the sepsis syndrome is provided elsewhere (Bone et al. 1989; Bone 1991b; Parrillo et al. 1990).

Previous work by Ziegler and colleagues demonstrated the ability of a human polyclonal antiserum to the core region of endotoxin to reduce the mortality associated with Gram-negative infections (Ziegler et al. 1982). This early work subsequently led to the development of 2 monoclonal antibodies directed at the same target. Nebacumab (HA-1A, Centoxin) produced by Centocor is a human monoclonal IgM antibody that binds to the lipid A core of endotoxin (Teng et al. 1985). ES produced by Xoma is a murine monoclonal antiendotoxin antibody with similar binding activity (Harkonen et al. 1988) Recent clinical trials with these agents demonstrate their ability to alter the sepsis process by binding endotoxin, thus reducing the morbidity and mortality associated with serious Gram-negative infections in selected patient groups (Greenman et al. 1991; Ziegler et al. 1991a). However, lack of agreement about the population of patients most likely to benefit from therapy in the published trials with these agents has fuelled considerable debate concerning their use (Bone 1991a,c). Although most authors agree that these products should not be administered to every patient with a clinical picture of sepsis, general consensus has not been reached with respect to specific guidelines for their use (Bone 1991c). In addition, detailed information pertaining to the prevention of or reduction in overall morbidity, a potential source of overall cost savings, have not been reported outside of the original publications (Greenman et al. 1991; Ziegler et al. 1991a). This results in large part from absence of disease definitions of sepsis-related morbidity, and to our in-