Mediastinitis caused by anastomotic leaks is the most severe complication after esophagectomy and the major source of morbidity and mortality. It is characterized by local intrathoracic reactions (mediastinitis) and systemic extrathoracic reactions (sepsis). Consequently the therapeutic concepts are clearly defined. To achieve successful management, early diagnostic work-up is mandatory in every disturbance of the normal postoperative course. This includes direct endoscopic inspection of the anastomosis to evaluate the vitality of the anastomosed organs and the size of the leak. According to location and clinical classifications of the leak, the spectrum of therapeutic options ranges from simple drainage procedures, endoscopic interventions, and stent implantation to reoperation or discontinuity resection. In any case the treatment goals must be immediate and sufficient drainage of the leakage and hindrance of further contamination across the leakage by gastrointestinal content. Also mandatory is the early initiation of supportive systemic strategies according to pathophysiologic principles of sepsis. The fundamental requirements for successful management are therefore aggressive local intervention and application of new concepts in sepsis therapy.