Candidal mediastinitis is rare. We report nine cases encountered at our institutions since 1985; seven cases were diagnosed since 1993. All cases followed thoracic surgery, with a median time from surgery to disease onset of 11 days (range, 6–100 days). All patients received prior antibiotic therapy. Common clinical manifestations were chest wall erythema in 4 cases (44%), drainage in 5 (56%), fever in 4 (44%), and sternal instability in 4 (44%). Failure to obtain appropriate intraoperative specimens for cultures and the dismissal of cultures positive for Candida as contaminants delayed diagnosis in three cases (33%). Mediastinitis was complicated by contiguous or hematogenous spread in seven cases (78%); five patients (56%) had two or more complications. The mortality rate was 56%. Optimal therapy remains undefined, but on the basis of our experience, aggressive surgical debridement combined with antifungal therapy for at least 6 weeks is recommended. Prompt recognition and institution of therapy appear to be the keys to improving prognosis.

Candida is a rare cause of mediastinitis, causing only 5% of cases reported in the English-language literature [1–13]. Although an increase in individual case reports of candidal mediastinitis has appeared in the literature since 1990 [14–17], the understanding of the disease and its optimal management remain limited by the small number of reported cases, the lack of a consistent definition of mediastinitis, incomplete clinical descriptions and accounts of therapy, and inadequate long-term follow-up of patients. Given the high morbidity and mortality rates associated with candidal mediastinitis [14], a comprehensive review of the clinical manifestations, natural history, microbiology, therapy, and outcome of the disease is needed.

Our experience with five cases of candidal mediastinitis from 1995 to 1996 prompted us to conduct such a review. A search for all cases at our institutions since 1985 confirmed the impression of its increasing incidence: of nine cases identified, 78% were diagnosed since 1993. In addition, we identified seven cases previously reported in the English-language literature that fulfilled our rigorous definition of candidal mediastinitis (see under Methods). We present our series of nine cases and review the literature to provide more complete insight into this emerging clinical entity.

Methods

Potential cases of candidal mediastinitis diagnosed at the University of Florida College of Medicine (Gainesville) and the Veterans Administration Medical Center (Gainesville) between 1985 and 1996 were identified via infection control files and medical record discharge code. Chart reviews determined that eight cases fulfilled our criteria for candidal mediastinitis (see under Inclusion Criteria). An additional case meeting the criteria was identified in a prospective study of candidemia that we conducted [18].

We also reviewed the previously reported cases of candidal mediastinitis in the English-language literature from 1966 to 1996 by using MEDLINE. Key words used were Candida, fungus, mediastinitis, pericarditis, sternal, and osteomyelitis.

Inclusion Criteria

Cases in our series met the following criteria: mediastinitis—infected of the region within the thorax between the pleural sacs that is bounded inferiorly by the diaphragm, superiorly by the apertura of thorax, anteriorly by the sternum and costal cartilages, and posteriorly by the thoracic vertebrae [19]; and Candida-positive culture of a specimen obtained intraoperatively or by guided biopsy from within the mediastinum.

Superficial wound infections following median sternotomy or thoracotomy were excluded, as were cases of sternal osteomyelitis, endocarditis, pericarditis, or empyema without evidence of extension into the mediastinum.

Results

From January 1985 to August 1996, eight cases of candidal mediastinitis were identified at our institutions. The clinical data for these patients and another patient identified during our prospective study of candidemia [18] are summarized in tables 1 and 2. These nine cases formed the database for our analysis.

Seven cases in our series were diagnosed since 1993. During this period, 3,061 cardiothoracic surgical procedures were performed at our institutions; the incidence of candidal mediastinitis was 0.3%.
Table 1. Clinical features of nine patients with candidal mediastinitis at the University of Florida College of Medicine (Gainesville) and the Veterans Administration Medical Center (Gainesville).

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, sex/year of diagnosis</th>
<th>Type of surgery</th>
<th>Time from surgery to onset of mediastinitis</th>
<th>Prior antibiotic therapy</th>
<th>Clinical findings</th>
<th>Prior or concomitant bacterial infection</th>
<th>Culture specimens positive for Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64 y, F/1985</td>
<td>Mitral and aortic valve replacement</td>
<td>11 d</td>
<td>Yes</td>
<td>Chest wall erythema, drainage, and instability, fever</td>
<td>Prior bacteremia with Proteus mirabilis and Enterococcus</td>
<td>Intraoperative mediastinal fluid, blood, sternum, urine</td>
</tr>
<tr>
<td>2</td>
<td>Newborn, F/1985</td>
<td>Blalock-Taussig shunt procedure</td>
<td>6 d</td>
<td>Yes</td>
<td>Chest wall erythema, drainage, and instability, shock</td>
<td>None</td>
<td>Intraoperative mediastinal fluid, chest tube, pericardial fluid, urine</td>
</tr>
<tr>
<td>3</td>
<td>74 y, M/1993</td>
<td>CABG, VSD repair</td>
<td>8 d</td>
<td>Yes</td>
<td>Chest wall tenderness, shock, fever, respiratory distress</td>
<td>None</td>
<td>Intraoperative mediastinal fluid/ thrombus, blood, sternum, pleural fluid</td>
</tr>
<tr>
<td>4</td>
<td>Newborn, M/1994</td>
<td>Heart transplantation</td>
<td>6 d</td>
<td>Yes</td>
<td>Open sternum, shock</td>
<td>None</td>
<td>Intraoperative mediastinal fluid, sternum; pleural, pericardial, and peritoneal fluids</td>
</tr>
<tr>
<td>5</td>
<td>59 y, M/1995</td>
<td>CABG</td>
<td>4 w</td>
<td>Yes</td>
<td>Chest wall erythema, drainage, and stability</td>
<td>None</td>
<td>Intraoperative mediastinal fluid, chest tube drainage</td>
</tr>
<tr>
<td>6</td>
<td>59 y, M/1995</td>
<td>Aortic valve replacement</td>
<td>13 d</td>
<td>Yes</td>
<td>Chest wall erythema, swelling, drainage, instability, and dehiscence</td>
<td>None</td>
<td>Intraoperative mediastinal fluid, blood, sternum</td>
</tr>
<tr>
<td>7</td>
<td>9 mo, F/1995</td>
<td>Blalock-Taussig shunt procedure</td>
<td>100 d</td>
<td>Yes</td>
<td>Sternal instability and click, fever</td>
<td>None</td>
<td>Intraoperative mediastinal fluid/ hematoma, polymeric silicone band, thrombus from graft, sutures</td>
</tr>
<tr>
<td>8</td>
<td>72 y, M/1996</td>
<td>CABG</td>
<td>8 d</td>
<td>Yes</td>
<td>Sternal instability and click, persistent wound drainage</td>
<td>Concomitant wound infection with Pseudomonas, Acinetobacter, and Staphylococcus aureus</td>
<td>Intraoperative mediastinal fluid and wound</td>
</tr>
<tr>
<td>9</td>
<td>50 y, M/1996</td>
<td>Esophagectomy with subsequent leak</td>
<td>26 d</td>
<td>Yes</td>
<td>Fever, subcutaneous emphysema</td>
<td>None</td>
<td>Percutaneous mediastinal fluid aspiration, chest tube drainage</td>
</tr>
</tbody>
</table>

NOTE. In case 9, the patient was infected with Candida glabrata. All other patients were infected with Candida albicans. CABG = coronary artery bypass grafting; S/P = status post; VSD = ventricular septal defect.

Patient Demographics and Underlying Conditions

In our series, there were six adults and three children. Two of the children were newborn infants. All three children had congenital heart disease; two children underwent a Blalock-Taussig shunt procedure, and the third underwent orthotopic heart transplantation. In the six adults, the most common underlying diseases (in descending order) were coronary artery disease (3 patients), valvular heart disease (2), and malignancy (1).

All nine patients underwent thoracic surgery prior to the development of mediastinitis. The median time between surgery and the onset of mediastinitis was 11 days (range, 6–100 days). Of note, the onset of mediastinitis in eight (89%) of nine patients occurred within 28 days of surgery; the onset occurred within 14 days in six (69%) of nine. All patients received antibacterial agents postoperatively. Three (33%) of nine patients were also treated with antibacterial agents for at least 4 days prior to surgery; all of these patients developed mediastinitis shortly after surgery.

Clinical Manifestations

The most common clinical manifestation was purulent drainage from the sternum (56%) (table 1). Fever, sternal instability, and chest wall erythema were each noted in 44% of patients. Other manifestations included shock (33% of patients), sternal click (22%), respiratory distress (11%), subcutaneous emphysema (secondary to esophageal rupture; 11%), wound dehiscence (11%), and sternal tenderness (11%).
### Table 2. Therapy and outcome for nine patients with candidal mediastinitis at the University of Florida College of Medicine (Gainesville) and the Veterans Administration Medical Center (Gainesville).

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Complication(s)</th>
<th>Initial antifungal therapy</th>
<th>Surgery</th>
<th>Response to treatment</th>
<th>Subsequent treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fungemia, sternal osteomyelitis</td>
<td>None</td>
<td>Debridement</td>
<td>No clinical response</td>
<td>NA</td>
<td>Died at 2 d</td>
</tr>
<tr>
<td>2</td>
<td>Fungemia, pericarditis</td>
<td>Amphotericin B</td>
<td>Debridement, removal of hardware</td>
<td>No clinical response</td>
<td>Added flucytosine</td>
<td>Died at 3 w</td>
</tr>
<tr>
<td>3</td>
<td>Fungemia, sternal osteomyelitis, empyema</td>
<td>Amphotericin B</td>
<td>Debridement, removal of hardware</td>
<td>No clinical response</td>
<td>Amphotericin B</td>
<td>Died at 9 d</td>
</tr>
<tr>
<td>4</td>
<td>Sternal osteomyelitis, pericarditis, empyema, peritonitis</td>
<td>Fluconazole</td>
<td>Debridement, removal of graft</td>
<td>No clinical response, with subsequent treatment</td>
<td>Fluconazole</td>
<td>Died at 2 mo</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>Amphotericin B for 2 w</td>
<td>Debridement, resection of clot</td>
<td>Clinical response</td>
<td>Fluconazole maintenance (400 mg q.d.)</td>
<td>Cured; 7-mo follow-up</td>
</tr>
<tr>
<td>6</td>
<td>Fungemia, sternal osteomyelitis</td>
<td>Amphotericin B for 2 w</td>
<td>Debridement, removal of surgical sternal wire</td>
<td>Clinical response</td>
<td>Fluconazole maintenance (400 mg q.d.) for 6 w</td>
<td>Cured; 14-mo follow-up</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>Fluconazole (20 mg b.i.d.) for 6 w</td>
<td>Debridement, removal of graft, sutures, and polymeric silicone bars</td>
<td>Clinical response</td>
<td>NA</td>
<td>Cured; 9-mo follow-up</td>
</tr>
<tr>
<td>8</td>
<td>Chronic wound infection</td>
<td>None</td>
<td>Five debridements, four vascular flap procedures</td>
<td>Persistent infection</td>
<td>Fluconazole maintenance (600 mg q.d.)</td>
<td>Ongoing infection; 5-mo follow-up</td>
</tr>
<tr>
<td>9</td>
<td>Empyema</td>
<td>Amphotericin B for 2 w</td>
<td>None</td>
<td>Relapse</td>
<td>Liposomal amphotericin B and flucytosine</td>
<td>Died at 2 mo</td>
</tr>
</tbody>
</table>

**NOTE.** MSOF = multiple system organ failure; NA = not applicable.

### Microbiology

All patients except one were infected with *Candida albicans*; one patient was infected with *Candida glabrata*. For eight (89%) of nine patients, *Candida* was isolated in pure culture. Cultures of specimens from within the mediastinum of all patients were positive for *Candida*. Other positive culture specimens included blood (44% of cases), sternal bone (44%), pleural fluid (22%), pericardial fluid (22%), urine (22%), thrombus (22%), wound site (11%), and hardware (11%). One patient had prior bacteremia, and another had concomitant bacterial infections of the mediastinum (table 1).

### Diagnosis

All patients had clinical evidence of mediastinitis. The diagnosis was subsequently confirmed by cultures positive for *Candida*. Chest radiographs were suggestive of mediastinitis in six (75%) of eight cases; these radiographs demonstrated a mass or fluid collection in four cases and mediastinal air in two.

For three patients, the diagnosis of candidal infection was not made until at least 3 weeks after the onset of mediastinitis; this delay was due to failure to obtain appropriate intraoperative specimens for culture (patients 1 and 5) or dismissal of cultures positive for *Candida* as contaminants (patient 8).

### Complications

Mediastinitis was complicated by either contiguous or hematogenous spread in seven (78%) of nine patients. Five (56%) of nine patients had two or more complications. Complications included fungemia (44% of patients), sternal osteomyelitis (44%), empyema (22%), pericarditis (22%), peritonitis (11%), chronic wound infection (11%), and infected thrombus (22%).

### Outcome and Therapy

The overall mortality rate was 56%; four (80%) of five deaths were directly attributable to candidal mediastinitis (tables 2 and 3).

Six patients were treated with combined surgical debridement and antifungal agents. Three of these patients died: two received amphotericin B therapy (patients 2 and 3) and one
received fluconazole therapy (patient 4). All three patients had multiple complications of candidal mediastinitis: fungemia (2 patients), pericarditis (2), sternal osteomyelitis (2), empyema (2), and peritonitis (1). The three surviving patients were treated with fluconazole alone (one patient) or with amphotericin B for 2 weeks followed by fluconazole for at least 6 weeks (two patients). These patients were doing well at 9-, 7-, and 14-month follow-ups, respectively.

Two patients who were treated with surgical debridement alone either died (patient 1) or developed chronic infection that ultimately required therapy with an antifungal agent (patient 8). The diagnosis was delayed for both patients: for patient 1, appropriate specimens for culture were not obtained during the initial surgery, and for patient 8, cultures positive for Candida were dismissed as contaminants.

One patient who was treated with antifungal therapy alone died despite treatment with liposomal amphotericin B and flucytosine (patient 9).

**Discussion**

Candidal mediastinitis is a rare clinical entity. The largest review of candidal mediastinitis, published in 1990, included 39 cases previously reported in the English-language literature [14]. Many of these cases, however, were superficial wound infections following sternotomy or infections of the sternum, costal cartilages, heart, pericardium, or pleura rather than true infections involving the mediastinum [20–27]. In addition, several reports failed to adequately provide clinical details, localize the precise site of infection, describe the method for diagnosis, or offer compelling evidence that Candida was contributing to disease [6, 7, 9, 14, 28–36]. We could identify only seven reports published since 1966 that provided a complete case description of a well-documented diagnosis of candidal mediastinitis [14–17, 37–40] (table 4). To this body of experience, we add our series of nine cases.

Seven (78%) of nine cases in this report were diagnosed since 1993, thus suggesting that mediastinitis due to Candida is an important emerging clinical entity. Our experience parallels an increase in individual case reports appearing in the literature since 1990 [14–17]. Whether the increase in case reports represents a true increase in the incidence of the disease or simply an increase in the recognition of Candida as a significant pathogen in the postsurgical population is not apparent. Although Candida has been implicated in outbreaks of wound infection following sternotomy [41, 42], there was no evidence that our increased number of cases was due to such an outbreak. Our cases occurred at two institutions, and no epidemiological links between cases were found.

All of our cases and six (86%) of seven previously reported cases followed thoracic surgery, which has been identified as the major predisposing factor for mediastinitis. In the era before cardiothoracic surgery, perforation of the esophagus was the leading cause of mediastinitis. In our series, only one patient developed candidal mediastinitis as a complication of an esophageal leak.

All our patients received antibacterial agents postoperatively; three (33%) of nine patients also received antifungal therapy for at least 4 days immediately prior to surgery. Prior receipt of antibacterial agents has been well established to be associated with candidemia and with nosocomial infection due to Candida.

One of the most surprising findings in our series was that six (67%) of nine cases occurred relatively early (within 14 days) after surgery. These observations suggest that the portal of entry is often direct intraoperative inoculation; indeed, direct inoculation was the attributed portal of entry in all patients in our series and in 15 (94%) of all 16 cases reviewed.

The most common clinical manifestations of candidal mediastinitis were chest wall drainage, erythema, sternal instability, fever, and shock. These findings were indistinguishable from those of bacterial mediastinitis. As such, Candida should be considered as a possible etiologic agent in any case of mediastinitis, especially those cases occurring in the setting of prior use of broad-spectrum antibiotics or those that do not respond to surgical debridement and therapy with antibacterial agents.

An appropriate level of suspicion is crucial to early diagnosis. All debrided or aspirated material should be sent for microbiological and histopathologic studies. The failure to appropriately obtain culture specimens from patients or the dismissal of cultures positive for Candida as contaminants led to delay in diagnosis in three (33%) of our nine cases; all of these patients died or subsequently developed chronic infections requiring multiple debridements and long-term antifungal therapy.

The mortality rate of 56% in our series was similar to that of 43% in the previous case reports. In our series, four (80%) of five patients with multiple (at least two) complications of candidal mediastinitis died; one (25%) of four with no or only one complication died. All survivors in our series and the pre-
Table 4. Summary of clinical data on seven patients with candidal mediastinitis previously reported in the English-language literature.

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Underlying condition(s)</th>
<th>Complication(s)</th>
<th>Initial antifungal therapy</th>
<th>Surgery</th>
<th>Response to therapy</th>
<th>Subsequent therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[37]</td>
<td>Esophagectomy, repair of esophagotracheal fistula</td>
<td>Fungemia</td>
<td>Miconazole</td>
<td>None</td>
<td>Persistent infection</td>
<td>Amphotericin B and flucytosine</td>
<td>Cured; 15-mo follow-up</td>
</tr>
<tr>
<td>[38]</td>
<td>CABG</td>
<td>Sternal osteomyelitis</td>
<td>Ketoconazole</td>
<td>Four debridements</td>
<td>None</td>
<td>Amphotericin B and debridements, ketoconazole maintenance</td>
<td>Stable condition while receiving maintenance therapy; 9-mo follow-up</td>
</tr>
<tr>
<td>[39]</td>
<td>Heart transplant</td>
<td>None</td>
<td>Amphotericin B</td>
<td>Debridements, repair of ruptured aortic aneurysm</td>
<td>None</td>
<td>Added flucytosine</td>
<td>Cured; 9-mo follow-up</td>
</tr>
<tr>
<td>[14, 40]</td>
<td>CABG, repeated thoracotomy due to hemorrhage</td>
<td>Sternal osteomyelitis, pericarditis, empyema</td>
<td>Amphotericin B</td>
<td>Debridements, pericardial stripping</td>
<td>Persistent infection</td>
<td>Muscle flap procedure</td>
<td>Cured; 9-mo follow-up</td>
</tr>
<tr>
<td>[15]</td>
<td>Boerhaave’s syndrome, esophageal repair</td>
<td>Fungemia, empyema</td>
<td>Amphotericin B</td>
<td>Debridements, esophageal repair</td>
<td>None</td>
<td>NA</td>
<td>Died at 1 mo</td>
</tr>
<tr>
<td>[16]</td>
<td>Cardiac surgery for congenital heart disease</td>
<td>None</td>
<td>Amphotericin B</td>
<td>Two debridements, muscle flap procedure</td>
<td>None</td>
<td>NA</td>
<td>Died at 1 mo</td>
</tr>
<tr>
<td>[17]</td>
<td>Anterior cervical fixation for spinal injury</td>
<td>Fungemia</td>
<td>Amphotericin B</td>
<td>Debridements, esophageal repair</td>
<td>No clinical response</td>
<td>NA</td>
<td>Died at 15 d</td>
</tr>
</tbody>
</table>

NOTE. CABG = coronary artery bypass graft; NA = not applicable.

Previously reported cases had significant morbidity, with prolonged hospitalizations, repeated debridements, and clinical relapses.

It is important to stress that the follow-ups in several previously reported cases were relatively short; therefore, any reports of cure must be interpreted with caution. It is not uncommon for apparently healed sternal wounds, in particular, to recurdesce months after cessation of therapy. As an example, a 42-year-old man with candidal mediastinitis associated with pericarditis and sternal osteomyelitis was described as cured at a 9-month follow-up after two therapeutic courses of amphotericin B and aggressive surgical debridement [40]. A subsequent report noted that 16 months later, his sternal wound infection recurred, and further therapy was required [14].

Evaluation of the optimal therapy for candidal mediastinitis is limited by shortcomings in the literature, particularly incomplete descriptions of antifungal regimens. On the basis of our experience, however, therapy combining aggressive surgical debridement with antifungal agents is the preferred approach to management of these infections. Early diagnosis offers the best chance to reduce subsequent morbidity and mortality. Vascular flaps have been touted as essential for cure [14], but in our experience, prompt diagnosis and aggressive therapy combining surgical and antifungal treatment appear to be the most important determinants of satisfactory outcome.

Conclusions

Increased recognition of Candida species as causes of bloodstream infection has been paralleled by increased appreciation of the role of these organisms in other nosocomial infectious processes. Candidal mediastinitis is one such process that has recently emerged as a significant cause of mortality and morbidity, particularly in patients undergoing thoracic surgery. This entity should be suspected in any patient with infection of the mediastinum, especially those cases occurring in the setting of broad-spectrum antibiotic use or those that do not respond to aggressive surgical debridement and therapy with antibacterial agents. It is of paramount importance that appropriate samples from any patient with suspected mediastinitis be sent for microbiological and histopathologic studies. Delay in diagnosis has been associated with poor outcome, including chronic wound infection, local extension involving the pericardium, pleural sac, and sternal bone, and hematogenous seeding. Mediastinitis complicated by these processes often is associated with a fatal prognosis. The optimal therapy for candidal medi-
Acknowledgments

The authors thank Robert Jenkins, Mary Ann Gross, Laura Natar dus, and Loretta Fauerbach for assistance in identifying cases, Robert Muder, M.D., and Victor L. Yu, M.D., for their thorough review and criticism of the manuscript, and Becky Godbey for assistance in manuscript preparation.

References