

Review Article

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Descending necrotizing mediastinitis in the elderly patients

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Abstract: Descending Necrotizing Mediastinitis (DNM) is a polymicrobial, dangerous and often fatal process, arising from head or neck infections and spreading along the deep fascial cervical planes, descending into the mediastinum. It can rapidly progress to sepsis and can frequently lead to death. It has a high mortality rate, up to 40% in the different series, as described in the literature. Surgical and therapeutic management has been discussed for long time especially in an elderly patient population. The literature has been reviewed in order to evaluate different pathogenesis and evolution and to recognise a correct therapeutic management.

Keywords: Descending necrotizing mediastinitis; Head and neck infection; Management

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1 Introduction

Descending necrotizing mediastinitis (DNM) is a critical infection of the mediastinal connective, involving median thoracic organs. This infectious process, of usually polymicrobial origin, is caused by downward dissemination of head and neck infections, especially from the mouth or pharynx (pharyngeal, peritonsillar, dental or odontogenic abscesses) through the facial spaces [1-14]. Pearse [15] first described the disease in 1938, utilising the term DNM. Hereafter, Estrera et al. [16] established criteria for the diagnosis of DNM, which involved:

1. Clinical evidence of severe oropharyngeal infection;
2. Radiologic evidence of mediastinitis;
3. Pathological evidence of necrotizing mediastinal infection at the time of surgery or autopsy;
4. Clear association between the descending necrotizing mediastinitis and the oropharyngeal-infection.

In this context, Endo, in 1999 proposed a classification, according to localization and severity of disease [17]: I) group I (disease limited to neck and upper mediastinum, until to tracheal carina); II) group IIA (disease extended to lower anterior mediastinum, below the tracheal carina); III) group IIB (disease extended to lower anterior and posterior mediastinum, below the tracheal carina).

DNM may occur in all of ages, from childhood to seniority. In the literature, heterogeneity of people affected by DNM range between 4 and 81 years old [18-21]. DNM diagnosis is frequently delayed because DNM symptoms are also common to other thoracic diseases arising from different pathways and expressing several biomolecular markers [22-52]. To date DNM remains an aggressive and sometimes-lethal disease in despite of the evolution of antibiotic therapy, advances in innovations in diagnostic and surgical techniques [53-70], and the development of intensive care protocols. Indeed, it is characterised by a mortality rate of up to 40% [20,21,71-77], and it is linked to rapid spread of head and neck infection and diagnosis and treatment can be delayed.

The infrequency of DNM has probably been one cause in its lethality. As in other uncommon disorders, prospective investigation of these patients is extremely difficult, and the patient's reported in literature are meagre and without classed data. In the view of this aspect, no precise therapeutic schema has been proposed and the optimal treatment for DNM is still discussed. First of all, reports are in according with broad-spectrum antibiotics use at the moment of the diagnosis. Agreeing to Endo classification and severity of disease, different surgical treatments have been suggested. However, the correct surgical choice appears controversial. We have reviewed the literature, in order to discuss and clarify which could be the optimal management for these patients.

2 Methods

The research was made by these key words: descending necrotizing mediastinitis, odontogenic infection, head and neck infection. We have utilised Pudmed/Medline. 189 papers were founded from the above research. We have excluded no english papers, case reports and we have included series containing five or more patients. We have thus evaluated 23 papers. They are presented in Table 1.

3 Results

Melero Sancho *et al* [78] reported the data of 7 patients, hospitalised between 1986 and 1997, affected by DNM, due to oropharyngeal infections (57% odontogenic infections, 43% peritonsillar abscess). Every patient was treated by bilateral cervicotomy, debridement and excision of necrotic tissue and a mediastinal drainage (4 transparietal drainage, one via sternotomy, one via thoracotomy, one via mediastinotomy). The authors concluded that DNM, early diagnosed by clinical and radiological signs, required an ample cervicotomy with mediastinal drainage, generally associated with thoracotomy. This surgical approach could significantly reduce the mortality rate.

Marty-Ane' *et al* [79], reported a 10 years' experience about DNM, consisting in 12 patients. The primary oropharyngeal infection was a peritonsillar abscess in 7 patients and an odontogenic abscess in 5 patients. The treatment proposed was bilateral cervicotomy in every patients, followed by a thoracotomic debridement and drainage in 11 cases and mediastinotomy and mediastinal drainage in one case. Author finally stated that, in patients with very limited disease to the upper mediastinum, tran-

scervical mediastinal drainage alone, was justified. For all the rest of patient with clinical or radiological signs of mediastinal infections or sepsis, drainage through a major thoracic approach, was required.

Freeman *et al* [80] reported the experience of 10 patients, in whom, descending necrotizing mediastinitis was identified. After radiological diagnosis by X-ray and CT scan, 5 patients was treated by transcervical drainage procedures, 3 by transthoracic drainage procedures. Three patients required abdominal exploration and 4 underwent tracheostomy. This paper clearly shows that, computed tomographic imaging for diagnosis and following serial transcervical and transthoracic operative drainages, are recognized such as correct algorithm in treatment of DNM.

Makeieff *et al* [77], analysed pre and postoperative outcomes of 17 patients, hospitalised in a single centre. DNM was due to pharyngitis (6 cases), peritonsillar abscess (3 cases), dental abscess (6 cases), foreign body infection (1 case), and laryngitis (1 case). Mean clinical manifestations duration before diagnosis, was 6 days. Only three cases performed the cervicotomy followed by the cervical and mediastinal drainage. In 14 other cases, a thoracotomic approach, with pleural and mediastinal cavity cleaning and debridement, was performed. Authors concluded that, correct surgical choice (usually thoracotomic approach with debridement and mediastinal and pleural drainage), corroborated to correct medical management in an intensive care unit, may significantly reduce the mortality rate to less than 20%. Similar data have been reported by Papalia *et al.* [1] and Mihos *et al.* [2].

Inoue *et al* [81] showed his series of patients, affected by DNM in the period between 1996 and 2004. Peritonsillar (77%) and odontogenic (23%) abscess were the originating infectious foci. Authors classified DNM in localized (infection localized to the upper mediastinum above the level of the carina) and extensive (infection extending to the lower mediastinum beyond the level of the carina). All patients underwent to surgical mediastinal drainage. In patients affected by extended DNM, simple mediastinal drainage was corroborated by a more aggressive approach and transthoracic drainage by right VATS or right thoracotomy. Authors suggested possibility of mediastinal surgical drainage alone, in limited DNM, and necessity of thoracoscopic or thoracotomic approach in extended DNM.

Iwata *et al* [82] analysed the data of 10 patients, treated in Inohana hospital. The causes of DNM were primary peritonsillar or parapharyngeal abscess (5 patients), odontogenic abscess (3 patients), one post-tracheostomy cervical abscess. One patient rested without primary diagnosis of infection spread. In this report, for the first time,

Table 1: Review of literature

Study	Period	Pat.	Primary infection	Topographic classification	Surgical treatment	Complications	Mort. rate	Risk factors
Melero-Sancho (67) Brazil	1986-1997	7	Odontogenic (57%) Peritonsillar (43%)	/	Transcervical mediastinum drainage (4) Transcervical + transthoracic drainage via thoracotomy (2) or sternotomy (1)	Thoracic wound infection (1) Septic shock (2) Renal failure (2)	14%	Not evaluated
Mart-Ané (68) France	1989-1999	12	Odontogenic (58%) Peritonsillar (42%)	/	Transcervical mediastinum drainage (1) Transcervical+Transthoracic mediastinum drainage via thoracotomy (11)	Septic shock (1) Reintervention (2)	16,5%	Not evaluated
Freeman et al (69) USA	1980-1998	10	Odontogenic (40%) Peritonsillar (30%) Retropharyngeal (30%)	/	Transcervical mediastinum drainage (5) Transthoracic mediastinum drainage via thoracotomy (3)	ARDS (4) Renal failure (2) Cardiac failure (2) Pneumonia (2) Reintervention (5)	29%	Not evaluated
Papalia et al (1) Italy	1994-2000	13	Odontogenic (46%) Peritonsillar (38%) Post-cervical trauma (16%)	/	Transcervical mediastinum drainage (3) Transcervical+Transthoracic mediastinum drainage via toracotomy (10)	Septic shock (3) Multi-organ failure (3) Reintervention (6)	23%	Not evaluated
Mihos et al (2) Greece	1980-2001	6	Odontogenic (50%) Peritonsillar (50%)	/	Transcervical+transthoracic mediastinum drainage via thoracotomy (6)	Septic shock (1) Multi-organ failure (1)	16%	Not evaluated
Makeieff et al (66) France	1984-1998	17	Pharyngitis (35%) Peritonsillar (17%) Odontogenic (35%) Foreign body (6%) Laryngitis (6%)	/	Transcervical mediastinum drainage (3) Transcervical+transthoracic mediastinum drainage via thoracotomy (14)	Septic shock (1) Pneumonia (14) Reintervention (3)	17%	Not evaluated
Inoue et al (70) Japan	1996-2004	13	Peritonsillar (77%) Odontogenic (23%)	Group I (6) Group II (7)	Transcervical (6) Transcervical+Transthoracic mediastinal drainage via VATS (2) or thoracotomy (5)	Thoracic wound infection (1) Pyothorax requiring reintervention (1)	8%	Diabetes Immuno-compety Chronic substance abuse (nicotine, alcohol)
Iwata et al (71) Japan	1991-2003	10	Peri-pharyngeal (50%) Odontogenic (30%) Post-tracheostomy (10%) Unknown (10%)	Group I (1) Group IIA (2) Group IIB (7)	Transcervical mediastinum drainage (1) Transcervical+Transthoracic mediastinum drainage via thoracotomy (9)	Septic shock (3) Reintervention (8)	20%	Not evaluated

continued Table 1: Review of literature

Guan et al (79) China	2001-2010	15	Odontogenic (100%)	Group I (11) Group IIA (4)	Transcervical mediastinal drainage (8) Transcervical+Transthoracic drainage via thoracotomy (4) and via VATS (3)	Septic shock (1) Multi-organ failure (1) ARDS (2)	6,7%	Not evaluated
Dajer-Fadel et al (80) Mexico	1994-2007	60	Odontogenic (45%) Retropharyngeal (25%) Cervical 11,7% Other (18,3%)	/	Transcervical + Transthoracic drainage via thoracotomy (60)	Septic shock (9) Pneumonia (15) Reintervention (8) Renal failure (3) Heart failure (4)	35%	Low socio-economic status
Palma et al (81) Italy	2007-2013	32	Odontogenic (64,7%) Peritonsillar (26,5%) Tonsillitis (8,8%)	Group I (14) Group IIA (10) Group IIB (10)	Transcervical drainage (14) Transcervical+Transthoracic drainage via subxiphoid or transcutaneous (10) or via thoracotomy (10)	Septic shock (4)	11,8%	11,8%

authors based the treatment on extension-severity's classification of Endo, in order to define limited or extended DNM. Nine patients presented an extended disease, with signs of infection until to posterior lower mediastinum. Surgical treatment consisted in cervical drainage, debridement and excision of necrotic tissue in the mediastinum and pleural decortication, via thoracotomy. Post-operative antibiotics irrigation with saline were performed in all cases, until negativizing of pleural liquid culture. 8 patients were discharged without post-operative complications and the mortality rate was 20%. Authors, thus recommended this combined surgical and medical treatment, regardless of extended or limited DNM.

Misthos et al [19] evaluated 27 patients, affected by DNM and treated between 1985 and 2002. All patients presented previous cervical phlegmon. According to Endo classification [7], patients were distributed into two groups, receiving different treatment. Specifically, patients with infection involving mediastinal tissue, until tracheal carina (group I classification Endo), underwent the combined transthoracic mediastinal and cervical drainage. Patients with extended DNM (group II classification Endo) underwent the debridement of any necrotic or infectious mediastinal tissue and the wide opening of mediastinal pleura, via lateral thoracotomy (the same side as the pleural effusion). In addition, they underwent the cervical drainage, via anterior cervical incision for performing debridement and excision of necrotic neck's tissue. The authors suggestion was that early combined thoracic and cervical approach could represent the treatment of choice for DNM.

Chen et al [83] showed Taiwan's experience (18 patients) in management of DNM. Odontogenic abscess (2 cases), peritonsillar or retropharyngeal abscess (9 cases), presence of foreign bodies (3 cases) and acute epiglottitis (3 cases) represented the primary infection focus. Surgical treatment for limited disease (11 patients) consisted in anterior cervicotomy with opening, draining and debridement of necrotic neck's tissue. A subsequent mediastinal drainage was posed via mediastinoscopy, VATS or subxiphoid access. Extended disease (7 patients) was treated by debridement of the mediastinum and pleura, excision and decortication of necrotic tissue and adequate placement of silicone drains or chest tubes. Chen concluded that simple mediastinal drainage was justified, only in the limited disease. For extended disease, an additional subxiphoid approach is suggested for anterior mediastinal involvement, while video-assisted mediastinal drainage is suggested for posterior mediastinum and pleural space.

Lanisnik et al [84] analysed descending necrotizing mediastinitis following to necrotizing fasciitis of the head

and neck. In 17 of 34 original patients with necrotizing fasciitis, it was diagnosed DNM. Here too, authors adapted surgical treatment to topographic localization of infectious focus. For DNM limited to upper mediastinum, until tracheal carina, (group I) it was performed a transcervical incision with mediastinum drainage and the chest tube positioning. For the diseases extended to lower anterior mediastinum (IIA), cervical drainage was completed by a transcervical mediastinum drainage; for disease extended to lower anterior and posterior mediastinum, it was performed a lateral thoracotomy in addition to cervical and mediastinal drainage. Finally authors remarked importance of early and accurate diagnosis for a correct therapeutic choice.

Thirteen patients were included in the report of Sokouti *et al* [20]. 10 cases had Mediastinal infection derived by odontogenic abscess and 3 cases had peritonsillar and retropharyngeal abscess. 8 patients underwent cervical drainage and thoracotomy, and 5 patients were treated by cervical drainage and mediastinotomy. Here too, authors underlined the importance of an early diagnosis.

Karkas *et al* [85] reported an experience of 17 patients with DNM. In ten patients, DNM was located above the carina and could be accessed by a cervical approach. In seven patients, DNM was below the carina. Particularly, patients with an anterior involvement were treated by sternotomy; those with posterior involvement were operated via postero-lateral thoracotomy. Authors finally drafted a therapeutic algorithm for the postoperative management of DNM.

A large series of DNM patients is reported by Deu-Martin [75]. 43 patients with a clinical and radiological diagnosis of DNM, deriving from head and neck infections, were enrolled. Surgical treatment was determined according to topographic classification of Endo. Authors analysed risk factors associated to DNM. Using bivariate and multivariate analysis, it emerged that age >66 years, associate comorbidities and diagnostic period (antecedent to 2000) represented the risk factors for post-surgical death. Finally they focused on early diagnosis and on necessity of multidisciplinary treatment.

Hsu *et al* [86] compared simple transcervical drainage alone for group 1 (limited disease) to integrated treatment (cervical and thoracic) for group 2 (extended disease). No difference in terms of post operative complications or death was observed but authors concluded that an aggressive, transcervical mediastinal drainage, associated to thoracic debridement is fundamental for a good outcome.

Ridder *et al.* [21] described another large series of patients. Author analysed 45 cases of DNM and he com-

pared his results with those resulting from a meta-analysis of 26 studies. The primary infection foci were pharyngeal infection, primary neck infection, odontogenic infection, ingested foreign bodies, iatrogenic pharyngeal perforation and iatrogenic catheter infection. All patients received cervicotomy for treating original infectious focus and trans-cervical drainage of the mediastinum. In only 7 patients a transthoracic approach to drain pleural cavity was performed (5 posterolateral thoracotomy, 1 sub-xiphoid approach and 1 sternotomy). Ridder concluded affirming that the formal thoracotomy should be reserved for cases extending below the plane of the tracheal bifurcation, according to Endo classification.

Wakahara *et al* [87] reported their experience, evaluating 11 patients with DNM. In all cases, regardless to severity of disease, patients were treated by an aggressive approach: cervical drainage by cervicotomy and subsequent lateral mini-thoracotomy or thoracoscopy (if possible), with toilette, debridement and decortication of infectious and necrotic tissue. Mortality rate was 0%. Authors finally recommended this approach in management of DNM.

Kocher *et al* [88] analysed surgical therapy and outcomes in DNM “Endo type II”. All 16 patients affected by DNM, were treated by an aggressive approach, 8 via sternotomy, 8 via clamshell. In addition, authors analysed risk factors in their population and they concluded that diagnostic-therapeutic delay (>15h from beginning of symptoms) represented a very important aspect to consider in the correct management. D’Cunha *et al* [89] proposed a cervical debridement for 8 patients admitted at Minneapolis Hospital. Guan *et colleagues* [90] examined two surgical treatments for DNM, involving anterior mediastinum (cervical drainage+ trans-cervical or transthoracic mediastinum drainage versus cervical drainage + bilateral thoracoscopy via sub-xiphoid access). 15 patients were enrolled and authors concluded that in these cases treatment by trans-cervical mediastinal drainages were possible. If mediastinitis spreads to the side of the trachea, an appropriate therapy is represented by open thoracotomy. If the entire anterior mediastinum is involved (over the trachea), cleaning and debridement should be performed with a thoracoscope via the subxiphoid incision.

Dajer- Fadel *et al* [91] reported the largest series in the literature on DNM. 60 patients were enrolled in this study during a 7-years period. All the patients underwent the drainage of three mediastinum compartment (upper, lower anterior and posterior) via postero-lateral thoracotomy, in order to debride and decorticate necrotic tissue of one or both pleural cavity and mediastinum. Authors analysed risk factors for mortality and they concluded that

age and diabetes were the most important risk factors, but, not for last, the socioeconomic level.

The only prospective study included in our review is the report of Palma et al [92]. Authors prospectively examined all patients with DNM admitted to the Intensive Care Unit. 34 patients were admitted and they were treated by trans-cervical drainage in DNM type I (14 cases, 42 %); patients affected by DNM type IIA (ten cases, 29 %), was treated by the anterior mediastinum irrigation through sub-xiphoid and cervical incisions, with additional percutaneous thoracic drainage when necessary; thoracotomy with radical mediastinal surgical debridement, excision of necrotic tissue and decortication was performed for patients affected by DNM type IIB (ten cases, 29 %). In addition, they founded an important correlation ($p=0,03$) between time to Intensive care unit admission after head and neck infection and pathological score (SAPS II score). Authors finally underlined the importance of an early assistance, aggressive surgery, and adequate antibiotic therapy for reducing mortality rate in DNM.

4 Discussion

Descending Necrotizing Mediastinitis arises from infectious process of usually polymicrobial origin, deriving and spreading from head or neck region, along the deep fascial cervical planes, descending into the mediastinum. It can rapidly progress to sepsis and frequently death.

From the analysis and review of literature, odontogenic abscess and peritonsillar abscess are the most common causes of DNM; other less frequent reported causes are parapharyngeal or retropharyngeal abscess, foreign bodies ingestion or penetration, acute epiglottitis, cervical trauma, acute pharyngitis or laryngitis, sinusitis, intravenous catheter infection and spinal corde abscess.

Clinical onset symptoms, frequently referred are: fever, cervical pain, dysphagia or odynophagia, dyspnoea and sepsis; swelling and dental pain, difficulty in opening the mouth and swallowing and jaw swelling are common in odontogenic and peritonsillar abscess. Cranial nerve deficits, linked to dissemination of necrotic and infectious tissue, may cause trismus and stridor [20].

The most frequent bacteria responsible for DNM are *beta-haemolytic Streptococcus*, *Staphylococcus aureus* and *Peptostreptococcus* for higher frequency of odontogenic or peritonsillar infections. Other frequent founded gram- bacteria are *Bacteroides*, *Pseudomonas aeruginosa*, *Enterobacter* and *Klebsiellapneumoniae*. More generally, there is not only one responsible bacterium, but a mixed

pool, consisting by both aerobic and anaerobic. Different nature of responsible microorganisms often reflected pharyngeal or odontogenic origins of this disease.

Most frequent post-operative complications, observed in the selected papers were septic shock, pleural empyema or pyothorax requiring reintervention, pneumothorax, cardiac arrhythmias, renal failure, multi-organ failure and thoracic wound infection. Mortality rate ranged between 0% [70,77,89] and 35% [91].

An attentive and careful analysis of selected papers, allowed us to investigate several points of interest.

Several surgical procedures have been proposed over years, for DNM management. However, Endo classification of 1999 [17] had represented the cornerstone in the management of this disease. Papers referring to surgical management of DNM, previous to this classification, proposed an aggressive approach consisting in mediastinum drainage and debridement of necrotic tissue, through thoracotomy, sternotomy or mediastinoscopy, but no specific surgical algorithm or rule has been recommended for these patients.

Endo et al. [17], for the first time described his classification, focusing on different topographic zones involved by infection; for every group, he proposed a different treatment, in according with gravity of disease. He established tracheal carina as topographic limit; particularly, classification provided for three different groups of patients, according to which, a different surgical approach put in place. Group I, consisted in cases with an upper mediastinum (until tracheal carina) involvement; in these circumstances, the simple radical cervicotomy with transcervical mediastinal drainage was justified. Group IIA consisted in the cases with a lower anterior mediastinal (beyond tracheal carina) involvement; suggested treatment in these situations was the radical cervicotomy and anterior mediastinal drainage through a subxiphoidal incision, or sternotomy. Sternotomy guarantees fast and simple access to the anterior mediastinum and both thoracic cavities. This approach allows one-stage procedure, avoiding patient repositioning (especially after prior cervicotomy).

However it allows limited access to the postero-basal mediastinum, especially on the left side. Group IIB, finally consisted in the cases with a lower posterior mediastinum involvement; in these cases radical cervicotomy had to be corroborated by posterior mediastinal drainage through right thoracotomy, and even through a contralateral thoracotomy in order to clean and drain all posterior mediastinum. Other reports [83,93,94] describe VATS as alternative technique. However, systematic debridement and opening (often necessary) of contralateral pleura and involved fascial spaces, which are indispensable to stop

infection and to prevent progressivity of the disease, are impossible, using VATS technique.

A conservative approach (cervicotomy and trans-cervical drainage) is justified only in DNM involving upper mediastinum (group I). In other cases, a radical and aggressive surgical treatment, consisting by right or left thoracotomy (group IIB), sternotomy or clamshell approach (group IIA and IIB), in order to debride and wash bilateral pleural cavities and mediastinum is recommended. Early identification of infectious involvement is fundamental, in order to avoid a diagnostic delay that seems to be a significant predictor of morbidity and mortality. In elderly, immune-deficiency and co-morbidities are major risk factor.

In particular, diabetes [95,96] and chronic substance abuse (eg, alcohol and/or nicotine abuse) [97] represents predisposing factors for developing DNM. Underestimation of the extent of disease and the influence of low socio-economic status may cause a delayed diagnosis or an insufficient therapy; represent other risk factors for promoting of infection's dissemination (Table 2).

The importance of a multidisciplinary approach should be considered in the DNM management. A close cooperation between anaesthesiologists, thoracic surgeons, pulmonologist, otolaryngologists and radiologists is required in order to assure the best assistance to patient. For all suspicions of DNM, an early and appropriate support or resuscitative therapy must be initiated. Intravenous broad-spectrum antibiotics (third-generation cephalosporin and metronidazole and/or clindamy-

cin or more generally penicillin and metronidazole) and airway management, represents the first step of treatment. An early antibiotic therapy, empirically begun on admission and later changed according to the microbiological examinations and antibiogram, is essential. Surgical clean up of the primitive infectious focus and the drainage and debridement of the neck and the mediastinum represents the second step in DNM management. Postoperative care plays a central role [6]. An appropriate and careful assistance by Intensive Care Unit is fundamental for these patients, in order to manage severe sepsis and/or septic shock and every possible complications, both at the beginning and after surgery [98].

A rapid CT scan control, corroborated by clinical and laboratoristic data, represents the cornerstone in the correct management of these patients. CT scan is the single most important tool for the early diagnosis of DNM and subsequent surgical drainage procedure but it is fundamental in the follow-up too; it can be helpful to evaluate the adequacy of surgical treatment or drainage, and to identify recurrent abscesses and progression of DNM, that required a quick return to operating room. Early, attentive and multidisciplinary approach can make a difference in the patient management.

5 Conclusions

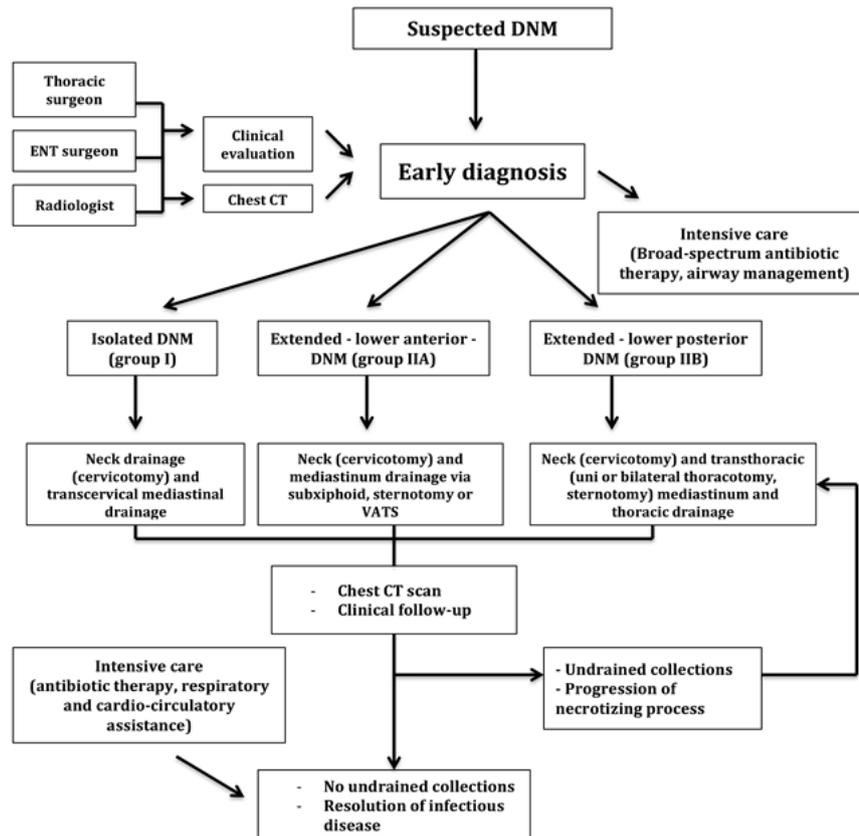
Descending necrotizing mediastinitis (DNM) is a critical infection of the mediastinal connective and it is a life threatening condition. A close cooperation between radiologists, intensivists, pulmonologists, oral and maxillo-facial surgeons and thoracic surgeons is required to best manage these patients. Early diagnosis, use of CT scanning to monitor the disease evolution, adequate supportive care in ICU and correct surgical treatment represent the crucial points for an appropriate management. However, DNM rests to be a dangerous, destructive and fatal disease, requiring the most attentive and careful assistance by therapists.

Conflict of Interests. The authors declare that they have no conflict of interests.

Table 2: Risk factors

Principal risk factors, associate to higher mortality rate
Delayed diagnosis
Immuno-competency
Co-morbidities (Diabetes)
Chronic substance abuse (alcohol, drugs)
Nicotine abuse
Low socio-economic status

Figure 1: Algorithm of review



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