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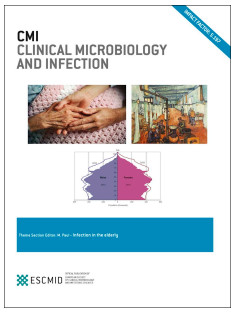

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Intensive Care Management of Influenza-Associated Pulmonary Aspergillosis

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Abstract

Background: Severe pulmonary infections are among the most common reasons for admission to ICU. Within the last decade increasing reports of severe influenza pneumonia resulting in acute respiratory distress syndrome (ARDS) complicated by *Aspergillus* infection were published.

Objectives: To provide a comprehensive review of management of influenza-associated pulmonary aspergillosis in patients with ARDS

Sources: Review of the literature pertaining to severe influenza-associated pulmonary aspergillosis. PubMed database was searched for publications since database inception until January 2019.

Content: In patients with lower respiratory symptoms, development of respiratory insufficiency should trigger rapid and thorough clinical evaluation, in particular in case of suspected ARDS, including electrocardiography and echocardiography to exclude cardiac dysfunction, arrhythmias and ischemia. Bronchoalveolar lavage should obtain lower respiratory tract samples for galactomannan assay, direct microscopy, culture, and bacterial, fungal and viral PCR. In case of positive *Aspergillus* testing, chest CT is the imaging modality of choice. If influenza pneumonia is diagnosed, neuraminidase inhibitors are the preferred approved drugs. When invasive aspergillosis is confirmed, first-line therapy consists of isavuconazole or voriconazole. Isavuconazole is an alternative in case of intolerance to voriconazole, drug-drug interactions, renal impairment, or if spectrum of activity including the majority of Mucorales is desired. Primary anti-mould prophylaxis with posaconazole is recommended in haematology patients at high-risk. It may be considered in newly diagnosed influenza and ARDS, but ideally in clinical trials.

Implications: The rising reports of influenza-associated pulmonary aspergillosis in patients with ARDS, who are otherwise not considered at risk for fungal pneumonia demands heightened clinical awareness. Tracheobronchitis and *Aspergillus* in respiratory tract samples should prompt suspicion of invasive fungal infection and further work-up. The management algorithm should comprise bronchoalveolar lavage, CT imaging, sophisticated ventilator-management, rescue extracorporeal membrane oxygenation, antifungal and antiviral therapy. In order to decrease the burden of influenza-related illness, vaccination is of utmost importance, specifically in patients with comorbidities.

Case vignette

A 46-year old woman without underlying disease was admitted with respiratory insufficiency due to influenza B pneumonia (Figure 1). Respiratory worsening despite appropriate supportive treatment required extracorporeal membrane oxygenation (ECMO).

Introduction

Incidence and mortality of influenza outbreaks vary annually, but have characteristic time courses with rising case numbers in winter season.[1] Re-assortment between influenza viruses leads to pandemics or seasonal epidemics with possible intercontinental distribution.[2-4] In seasonal influenza, 5 to 10 percent of a population are affected[5] and intensive care management is mandatory in severe pneumonia and acute respiratory distress syndrome (ARDS). Globally, an estimated 290,000 to 646,000 patients die due to seasonal influenza every year.[6] A recent publication challenges the common perception that influenza B in comparison to influenza A mainly causes mild illness.[7]

ARDS is characterized by diffuse inflammatory lung injury urging fast recognition and prompt treatment to improve outcome. Mostly, onset is within one week post an untoward event, but signs and symptoms are highly variable. Recently, increasing numbers of influenza-associated pulmonary aspergillosis (IAPA) are reported.[8-10] Potential reasons for this observation are manifold and comprise higher patient numbers at risk, older patients admitted to ICU, prolonged time at risk due to ECMO therapy that increases survival time and rate, improved diagnostic tools and greater awareness among ICU clinicians.[10-12] Influenza causes alveolar epithelial and endothelial damage, impaired mucociliary activity aggravated by immune cell dysfunction, and immune system dysregulation.[13-15]

Among patients with influenza-associated pulmonary aspergillosis, 90% needed mechanical ventilation, and 19% required ECMO.[10] Influenza A was the most common (86%) type found, while influenza B accounted for 14% of cases, respectively.[10] Risk factors for aspergillosis are well established in immunocompromised populations. However, 25% of reported patients were previously healthy like our case vignette.[10,16] At 90 days after ICU admission mortality rate of patients with IAPA was 51%.[10] The magnitude to which azole resistance adds to such excessive mortality is not fully understood.

In this review we provide an overview of the current understanding of the co-occurrence of influenza infection and pulmonary aspergillosis. We provide evidence-based expert guidance on the optimal intensive care management of IAPApatients, who often fall outside typical at risk populations.

Acute respiratory distress syndrome

Pulmonary bacterial or viral infections are often associated with severe ARDS and in many cases trigger septic shock and multiple organ failure. ARDS is a common and often lethal clinical syndrome with a complex underlying pathophysiology and diffuse inflammatory alveolar injury. Characteristics are acute onset of non-cardiogenic pulmonary oedema following increased alveolar capillary permeability resulting in profound hypoxemia. ARDS is one of the most common causes of ICU admission, and ARDS associated age-adjusted mortality is 2.82 per 100,000.[12] In 1994, the American-European Consensus Conference defined ARDS, which the Berlin Definition for ARDS revised in 2012.[17,18]

Besides causal treatment, mechanical ventilation employing lung-protective strategies represents the basis of ARDS management (Table 1).[19,20] If infection triggered ARDS, antimicrobial treatment is key. Sepsis and septic shock with multiple organ failure should be

104 treated according to the current 2016 sepsis guidelines.[21,22] As shown during the 2009 H1N1
105 pandemic, veno-venous (VV) ECMO can rescue patients when conventional ventilation
106 techniques fail (ECMO Indications, Table 2).[23]

107 One of the most prevalent causes of ARDS is influenza infection.[24] The observation of
108 influenza preceding secondary infections, suggests that influenza infection has broad and
109 long-lasting effects on the immune system.[25] Histology from fatalities of the 1918 pandemic
110 revealed bacterial pneumonia as principal cause of death.[26] Recently, it has been recognized
111 that influenza paves the way for fungal pathogens, too.[10] An animal model demonstrated
112 endogenous glucocorticoid production induced by influenza virus resulting in systemic
113 immunosuppression facilitating secondary bacterial infection.[25] It can be hypothesized that
114 systemic immunosuppression increases the risk of influenza-associated pulmonary
115 aspergillosis even with substantial delay, as in our case.

116

117 **Diagnostic algorithm**

118 According to the Berlin definition patients with acute respiratory failure fulfil several clinical
119 criteria, and are graded into mild, moderate and severe ARDS, based on the PaO2/FiO2-ratio
120 and positive end-expiratory pressure (Figure 2).[18]

121 If infection is suspected, rapid diagnostic work-up is crucial. A nasopharyngeal tract sample
122 for conventional influenza RT-PCR should always be obtained. Antigen testing and direct or
123 indirect antibody staining tests should only be used in settings lacking the more sensitive
124 molecular assays.[27]

125 Bronchoalveolar lavage or, if on ventilator support a lower respiratory tract sample should be
126 pursued to increase diagnostic yield and good sample quality.[27] Testing should comprise
127 galactomannan (GM), direct microscopy, culture, and specific bacterial (*Legionella* spp.,

Mycoplasma pneumoniae, Chlamydia pneumoniae, and Chlamydia psittaci), fungal and viral PCR (Figure 3). Fungal diagnostic assays with higher specificity in non-neutropenic patient cohorts are an unmet need. The advantage of bronchoscopy over blind suctioning of tracheal secretions is the visualization of trachea and bronchi. This is mandatory as up to 15% of patients develop tracheobronchitis with plaques and invasive and obstructive growth (Figure 4, Video 1).[9] Direct proof of tracheobronchitis can be absent or subtle in CT imaging.[9,28] In case of microbiological proof of *Aspergillus* infection, imaging modality of choice is chest CT, although its yield is highly variable and may be as low as 29%.[9] Specific signs, such as nodular lesions with halo are less common in non-neutropenic patients and principal findings can be segmental or wedge-shaped consolidation, nodular lesions with or without cavity or ground-glass opacities.[29]

GM is a major polysaccharide of the *Aspergillus* cell wall with its serum concentration related to angioinvasion and invasive fungal growth. *In vitro,* close relationship has been shown between fungal invasion of the endothelial cell layer, and simultaneous increase in GM levels.[30] Elevated serum GM levels indicate invasive aspergillosis and increased fungal burden. If invasive aspergillosis is suspected, we determine serum GM on three consecutive days to rapidly complete the diagnostic algorithm.[31,32] β-(1,3)-D-glucan is a fungal cell wall component that is not specific for *Aspergillus* spp. but also present in yeasts and bacteria. It can be useful to exclude fungal infection.[33] The additional use of lateral flow devices, where available, may support a diagnosis of invasive aspergillosis.[34]

Autopsy series show that strict interpretation of the host and risk factors for invasive aspergillosis according to the European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) definitions increases the risk of missed diagnosis.[35-37] A most difficult issue is the discrimination of *Aspergillus* colonization from invasive disease. While histopathology sets the gold standard to prove invasive disease, it is often

contraindicated. Radiological lesions in patients with ARDS are non-specific but a newly diagnosed cavitary lesion hints towards invasive aspergillosis. To discriminate colonization from true infection in a population which is not covered by the EORTC/MSG definitions a clinical algorithm for ICU patients was developed and a consensus project will seek to provide standard definitions for invasive fungal disease in critically ill adult patients.[38,39]

Performance of most invasive aspergillosis *in vitro* diagnostics differ in patients with and without neutropenia, and may again be different in influenza patients. Newer lateral flow devices are significantly less sensitive and particularly specific in a non-neutropenic cohort[34] when compared to haematological disease.[40] Overall, it is difficult to define invasive aspergillosis in non-neutropenic, non-haematological populations.

In case of missing response to systemic fungal treatment, biopsy or re-sampling should be considered to exclude triazole resistance or other entities mimicking ARDS.[41] Species identification to complex level is mandatory as some species are intrinsically resistant to either azoles or amphotericin B. Antifungal susceptibility testing of *Aspergillus* isolates preferably uses minimum inhibitory concentration (MIC) testing. If unavailable, routine agar screening may be used to detect azole resistance. Any resistant isolates should be referred to a mycology reference laboratory for MIC testing.[42]

Case vignette: diagnostic and treatment course

ECMO therapy was applied for 8 days in two episodes (Figure 1). In bronchoalveolar lavage fluid, influenza B PCR was repeatedly positive, as was *A. fumigatus* culture (azole susceptible). Chest CT revealed nodular infiltrates with surrounding halos (Figure 5, Video 2). Voriconazole treatment with 6 mg/kg body weight (BW) as loading dose and 4 mg/kg BW as maintenance with therapeutic drug monitoring was initiated. The patient was weaned from mechanical ventilation after 12 days. Eight weeks later respiratory deterioration required re-

intubation. Bronchoscopy revealed tracheobronchitis with considerable tracheal stenosis (Figure 4, Video 1). Corticosteroids were administered (2 mg/kg BW) when tracheal stenosis seriously obstructed the trachea. Biopsies showed necrotizing infection and *Aspergillus* invasion on histopathology.

Management bundle

Current guidance strongly recommends the prompt initiation of antiviral treatment for any patient hospitalized with influenza, particularly in case of severe and progressive illness, irrespective of influenza vaccination history.[43,44] Neuraminidase inhibitors (NAIs), i.e. oral oseltamivir, inhaled zanamivir or intravenous peramivir, represent the preferred and approved drugs in this setting.[43] Recommended schedules are the following: Oseltamivir 75 mg every 12 hours (with dose adjustments based on body weight and renal function), inhaled zanamivir 10 mg every 12 hours, or intravenous peramivir administered as a single dose of 600 mg infusion. Five days of treatment are usually suggested, although longer durations should be considered among patients presenting with severe lower respiratory tract disease or in the immunocompromised. Reasons for longer therapy in the immunocompromised are higher viral load, prolonged shedding and variable drug bioavailability due to graft-versus host disease or chemotherapy-associated gastrointestinal malabsorption.[45] Combination of different NAIs, as well as increased dosages, are currently not recommended nor supported by any evidence. However, based on pharmacokinetic data, higher doses of oseltamivir (105 mg or 150 mg every 12 hours) have been suggested in pregnant women.[43] The use of intravenous peramivir has been associated with a survival rate of 62% among patients with severe influenza admitted to ICU; no significant differences in terms of mortality have been described with peramivir compared to oseltamivir.[46,47] Some studies reported different efficacy of oseltamivir treatment by influenza virus type, with higher efficacy rates reported

in patients with H3N2 infection.[48] Whether antiviral treatment of influenza pneumonia affects the occurrence of secondary lung infections is currently unknown, since to date no published studies investigated this topic. The use of corticosteroids has no beneficial effect – but was shown to be associated with longer duration of ventilation, increased rates of acquired pneumonia and higher mortality.[49]

Early administration of antifungal therapy in critically ill patients with invasive aspergillosis is of outstanding importance and has been associated with significant reduction in mortality rates and improvement of clinical outcomes.[50] However, diagnosis of invasive aspergillosis in patients with influenza represents a challenge in clinical practice due to the low clinical suspicion among non-immunocompromised hosts and the lack of specificity of both clinical and radiological features.[29,38] These difficulties cause delays in effective antifungal treatment, and increase mortality. Rates reported may be higher than 65%, and a substantial proportion is diagnosed only *post-mortem*.[51,52] When invasive aspergillosis is diagnosed, isavuconazole (loading dose 200mg TID iv for two days (six administrations), from day 3 200mg QD iv (12 to 24 hours after last loading dose administered) or voriconazole (loading dose 6mg/kg BW BID iv on day one, from day two 4mg/kg BW BID iv), currently represent the first-line recommended options.[42] While in many settings isavuconazole is more costly than voriconazole, key advantages of isavuconazole over voriconazole or liposomal amphotericin B are: 1) favourable tolerability profile, especially for patients with acute kidney injury[53,54]; 2) reduced risk of QTc interval prolongation[55]; 3) broader spectrum of activity, including most of the *Mucorales* order with species-specific and method-dependent differential activity[56-58]; 4) reduced risk of drug-drug interactions.[31] Liposomal amphotericin B (3mg/kg BW QD iv), posaconazole (loading dose 300mg BID iv on day one, from day two 300mg QD iv) and echinocandins are considered second-line options in refractory cases or when voriconazole or isavuconazole are contraindicated.[42] Failure of (initial) azole therapy may be due to insufficient azole drug levels or azole resistance, which is now commonly found (>20%) in

several centres especially in Europe and significantly complicates the management of aspergillosis[8,10,59,60] In case of *Aspergillus* isolates with voriconazole MIC ≥2, switch to another drug class is recommended, and combination of voriconazole plus echinocandin has been proposed.[42,60] In case of disease progression after therapy initiation (refractory disease) a switch to another drug class e.g. to liposomal amphotericin B (3mg/kg QD iv) or an echinocandin is recommended.[42] Therapeutic drug monitoring is recommended to achieve effective and safe drug exposures as this patient population often show decreased absorption, limited distribution, altered metabolism or clearance of antifungal medications or receive other substances potentially interacting.[42] For voriconazole a plasma trough concentration of 1-5.5 mg/L is recommended.[42] In case of posaconazole levels of 0.5-3.75 mg/L are considered safe and effective with all three formulations (suspension, tablet and intravenous formulation).[42] For isavuconazole no recommended level is available to this date, however the possible cause of treatment failure, drug interactions, or if toxicity may be elucidated by TDM.

The use of steroids has been associated to the increased mortality among patients with IAPA admitted to ICU and its use therefore is not recommended in this setting.[61]

Prevention

Vaccination represents the most effective tool to reduce the burden of influenza-related illness.[62] Although reported influenza vaccine effectiveness is approximately 40%, with significant variations with regard to different influenza serotypes, vaccination has been associated with a reduction of influenza-associated morbidity, medical visits, hospitalizations and deaths.[62] Currently, the Centers for Disease Control and Prevention recommend influenza vaccine for everyone (6 months of age and older) in every season. However, vaccination is

particularly important and even essential for people who are considered at high risk of serious complications from influenza, particularly children younger than 2 years and adults aged 65 years and older, pregnant women, residents of nursing homes and long term care facilities and people with underlying chronic medical comorbidities.[63] Incidence of IAPA among critically ill patients has been reported to be significantly higher in immunocompromised patients with the 'classic' risk factors for invasive aspergillosis according with European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) definitions compared with the ones without underlying immunosuppression (32% versus 14%).[10,37] However, a significant burden of cases of IAPA has been reported in patients without significant comorbidities and not considered at high-risk for influenza complications.[10] For this reason, universal vaccination programs, with the prioritization of high-risk categories, might probably represent the most effective tool to reduce the incidence of IAPA among critically ill patients.

Primary anti-mould prophylaxis with posaconazole (oral suspension 200 mg every 8 hours or tablet formulation 300 mg every 24 hours) is strongly recommended for reducing incidence of invasive aspergillosis in haematological patients belonging to high-risk categories (e.g. patients with acute myeloid leukaemia and allogenic hematopoietic stem cell transplantation with moderate or severe graft versus host disease and/or intensified immunosuppression).[42] Anti-mould prophylaxis might be considered in selected cases also in other haematological diseases[64], in solid organ transplant recipients, in HIV infected patients and in patients with chronic obstructive pulmonary diseases when specific risk for development of invasive aspergillosis exist.[42] Anti-mould prophylaxis in patients with newly diagnosed influenza and ARDS without underlying conditions can be discussed. However the high propensity for drug-drug interactions and unfavourable tolerability profile with voriconazole, the high costs of isavuconazole and the high number needed to treat make an empirical treatment approach

more reasonable and feasible. If a prophylactic approach is followed, it should always be done in clinical trials.

Clinical vignette resolution

After tracheostomy, needed to secure the obstructed airway, granulation and necrosis were surgically debrided. Due to progression of the tracheobronchitis during prior voriconazole treatment (30 days), therapy was switched to liposomal amphotericin B 3mg/kg iv and continued for 3 months. However, despite resolution of the infection, the patient continued to experience respiratory distress due to stenosis of the trachea (Figure 6), leading to definitive surgical resection of the stenosis. Subsequently, the tracheostomy tube was replaced by a spacer and the patient was discharged on posaconazole on day 188 and followed up as outpatient. This patient's clinical course illustrates the clinical significance of influenza-associated pulmonary aspergillosis with tracheobronchitis..

Conclusion

The rising numbers of reports of influenza-associated pulmonary aspergillosisin patients with ARDS, who are otherwise not considered at risk for fungal pneumonia, should raise clinician awareness. Patients with ARDS should be considered at increased risk for opportunistic pulmonary infections, particularly with *Aspergillus* species. Why patients with influenza are at risk for invasive pulmonary aspergillosis is not yet clear but influenza-induced ARDS and hypoxia might cause immune paralysis predisposing for this infection. In addition to critical care management with lung-protective ventilation strategies and provision of ECMO as needed, patients with ARDS need close monitoring for signs of secondary pulmonary infections. Tracheobronchitis and growth of moulds from respiratory tract samples are

important and prompt further work-up. If secondary infections are detected, appropriate antinfectives should be initiated quickly. Importantly, vaccination against influenza, especially in patients at higher risk and their contact persons is mandatory to protect patients from ARDS and secondary complications and thus to reduce morbidity and mortality.

Consent to participate

The patient gave her written informed consent regarding her case report to be published.

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This study was carried out as part of our routine work.

Transparency declaration

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Matteo Bassetti has participated in the past five years in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, BioMérieux, Cidara, Gilead, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRx, and Vifor.

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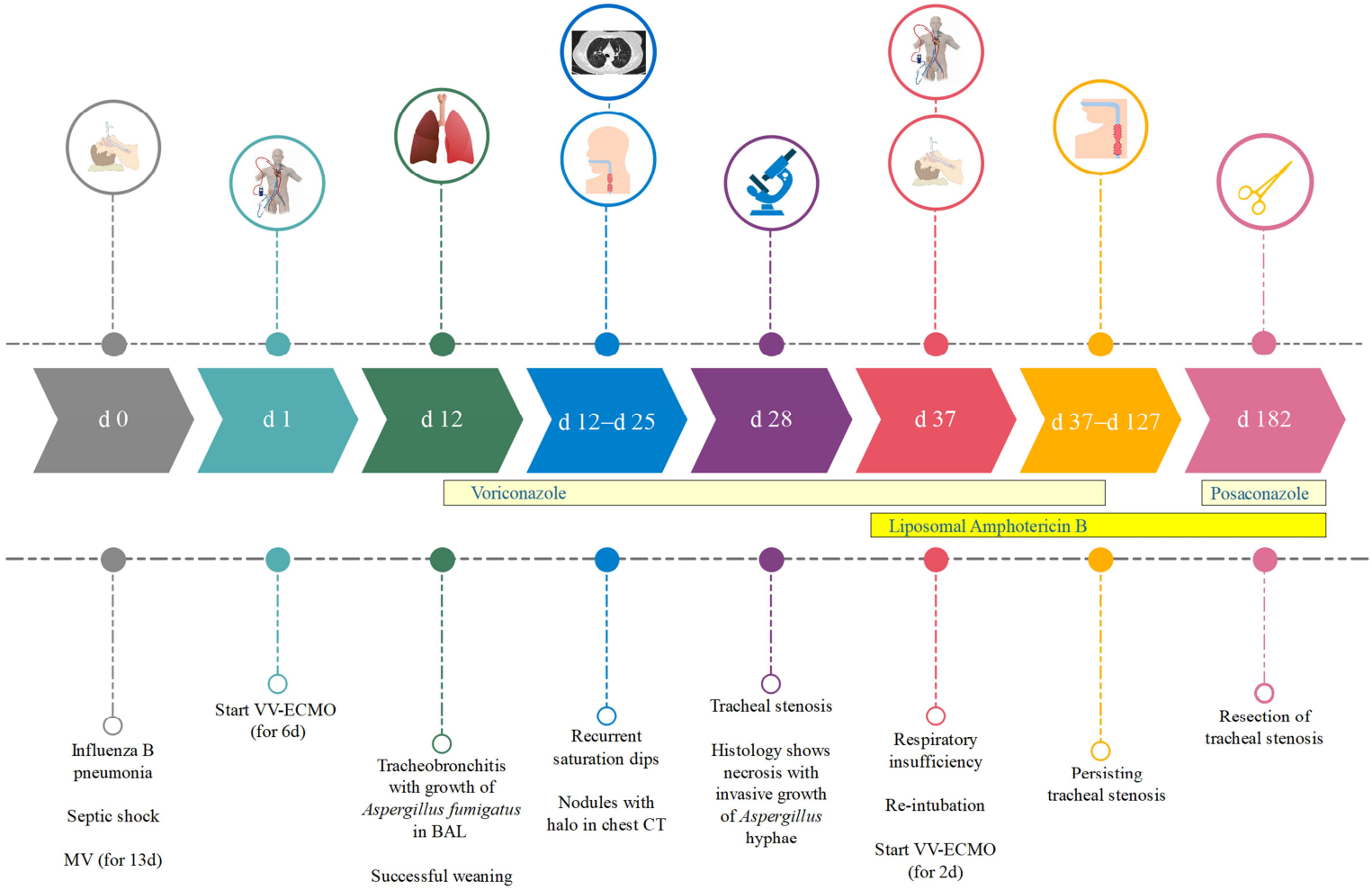
d 0
d 1
d 12
d 12–d 25
d 28
d 37
d 37–d 127
d 182
Voriconazole
Posaconazole
Liposomal Amphotericin B
Influenza B pneumonia
Septic shock
MV (for 13d)
Start VV-ECMO (for 6d)
Tracheobronchitis with growth of *Aspergillus fumigatus* in BAL
Successful weaning
Recurrent saturation dips
Nodules with halo in chest CT
Tracheal stenosis
Histology shows necrosis with invasive growth of *Aspergillus* hyphae
Respiratory insufficiency
Re-intubation
Start VV-ECMO (for 2d)
Persisting tracheal stenosis
Resection of tracheal stenosis

Figure 1. Clinical course of the case vignette patient. MV=Mechanical ventilation; VV-ECMO=veno-venous extracorporeal membrane oxygenation; BAL=Bronchoalveolar lavage; CT=computed tomography; d=days.

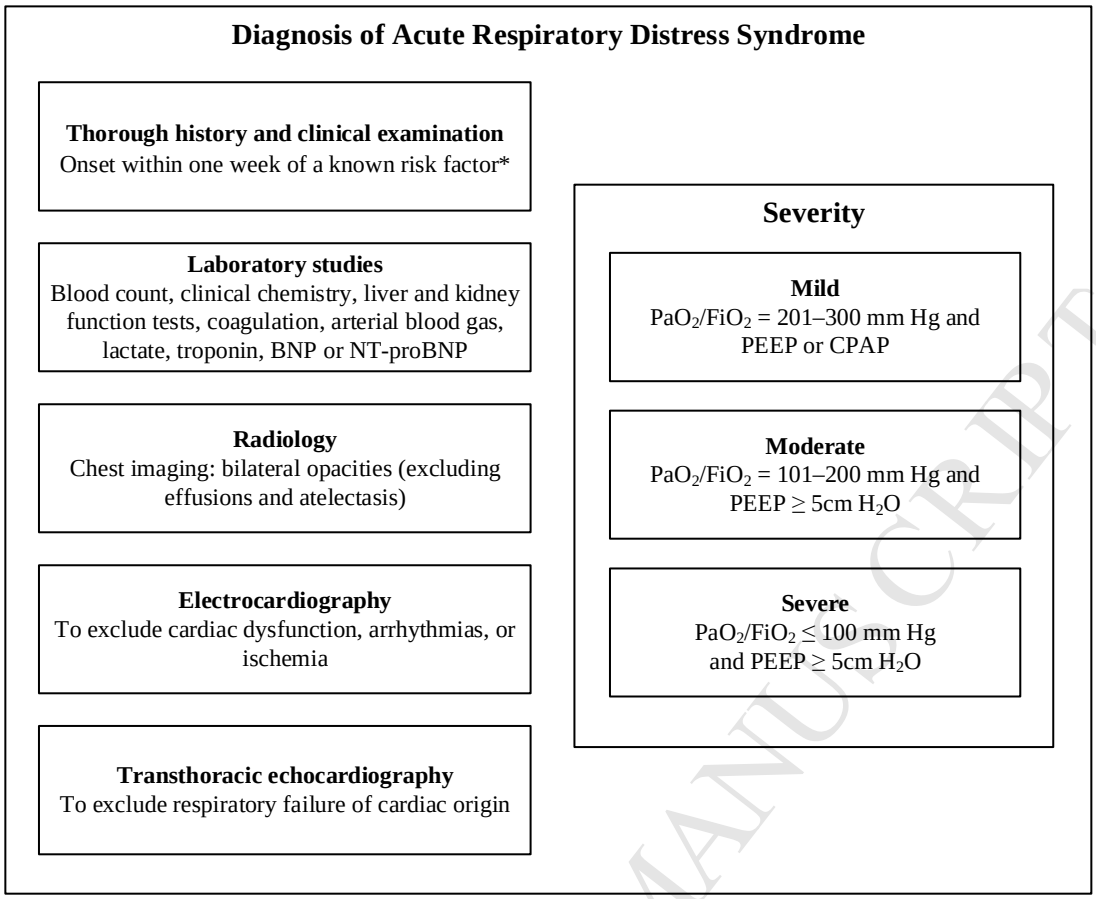

Figure 2. Diagnosis of acute respiratory distress syndrome – adapted from [23]

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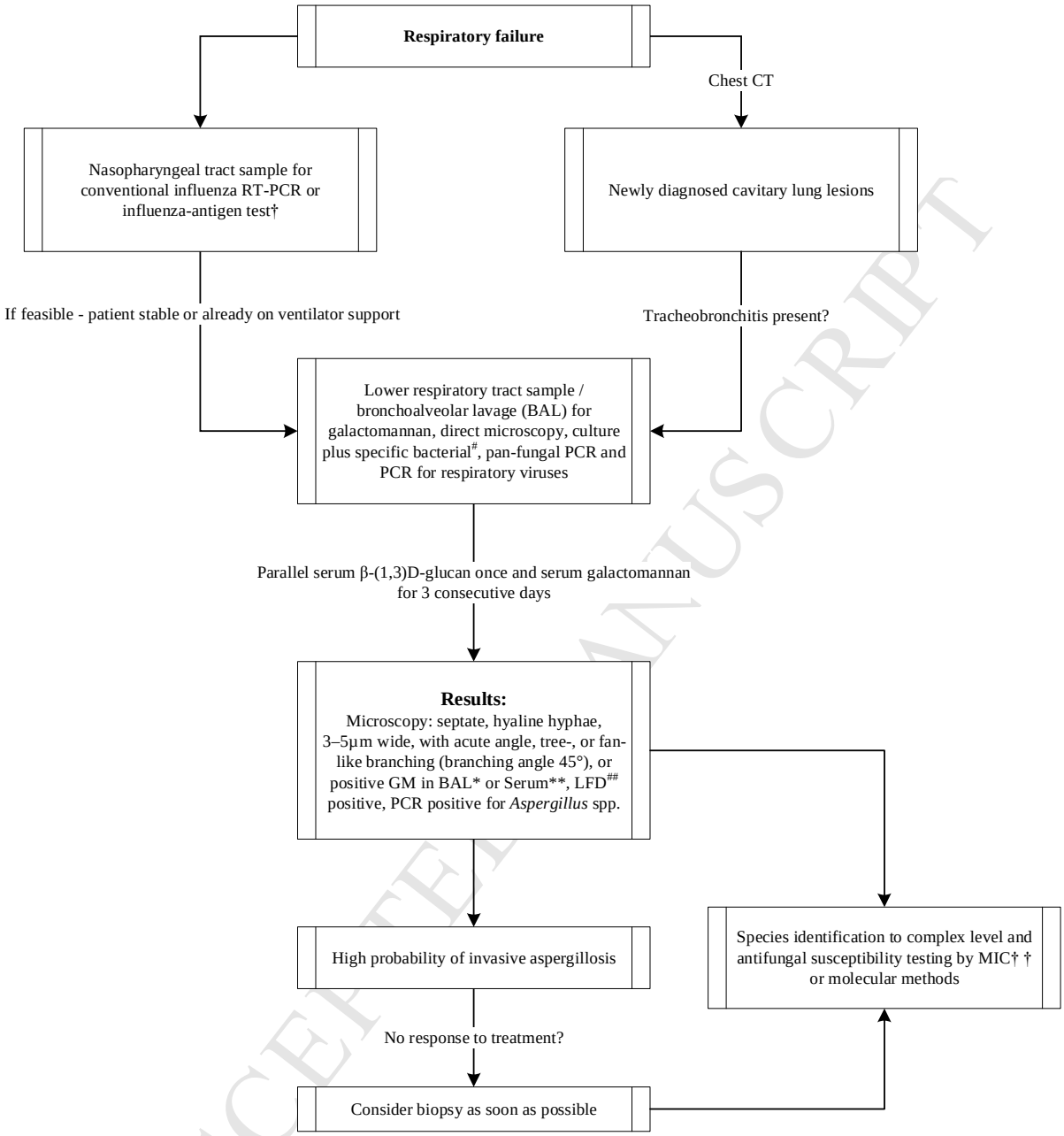

Figure 3. Management algorithm.

Optical brighteners should be used in any sample to detect fungal hyphae. †Antigen testing, direct or indirect antibody staining tests should only be used in hospitalized patients if more sensitive molecular assays are not available.[27] #*Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Chlamydia psittaci*, ##*if available*, *Galactomannan ODI in BAL cut-off: 0.5 to 1.0[42],

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GM=Galactomannan; LFD=Lateral flow device; MIC= minimum inhibitory concentration, RT-PCR=real-time reverse-transcriptase polymerase chain reaction

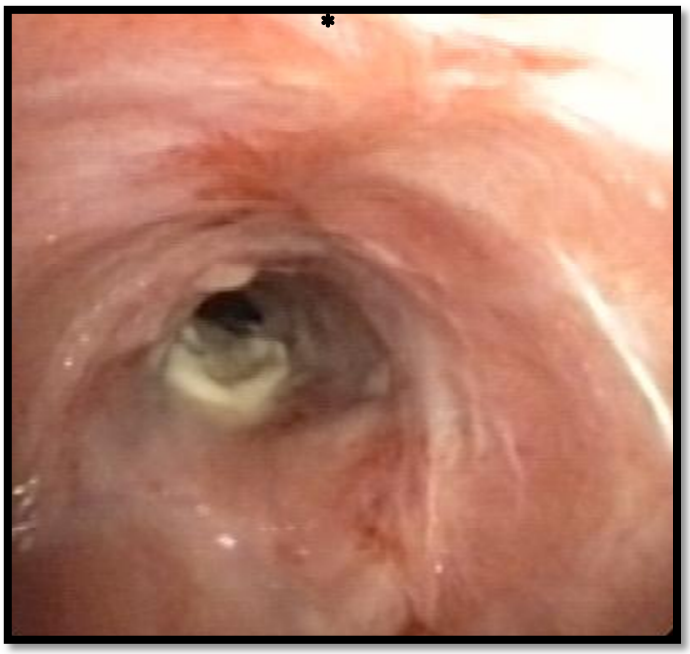

Figure 4. Tracheobronchitis with obstruction in bronchoscopy. *ventral wall.

Video 1. Bronchoscopy of tracheobronchitis with obstruction

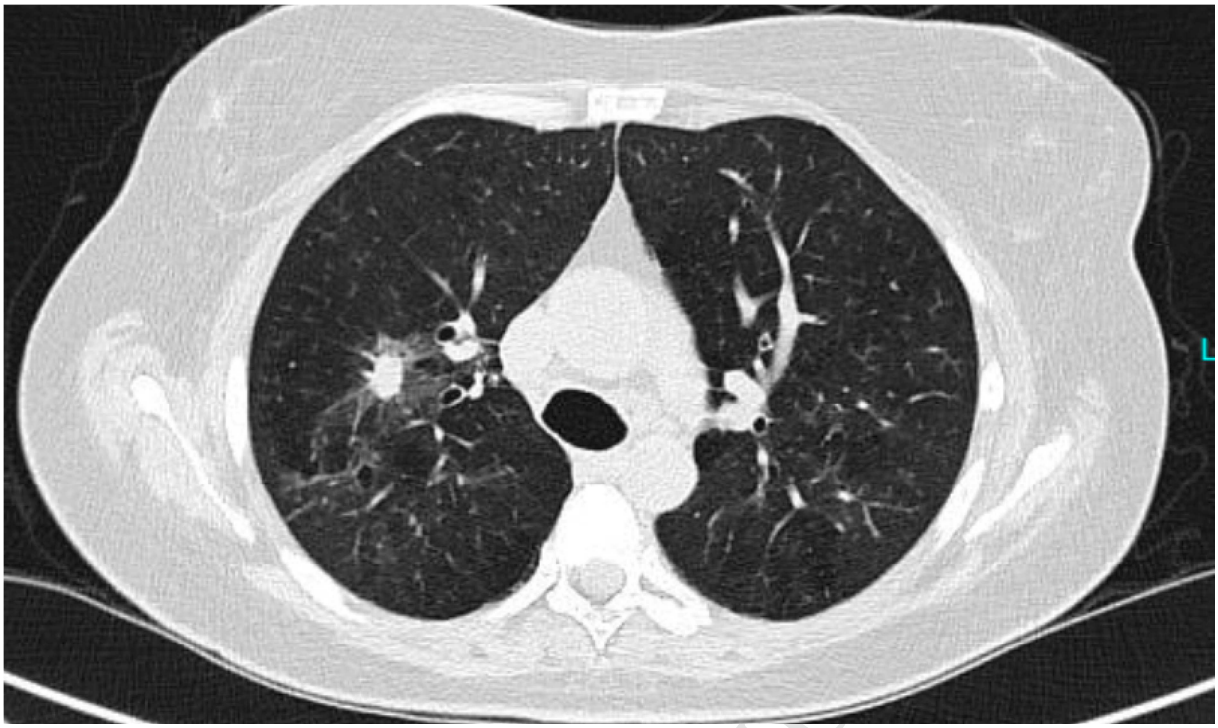

Figure 5. Chest computed tomography.

Video 2. Chest computed tomography

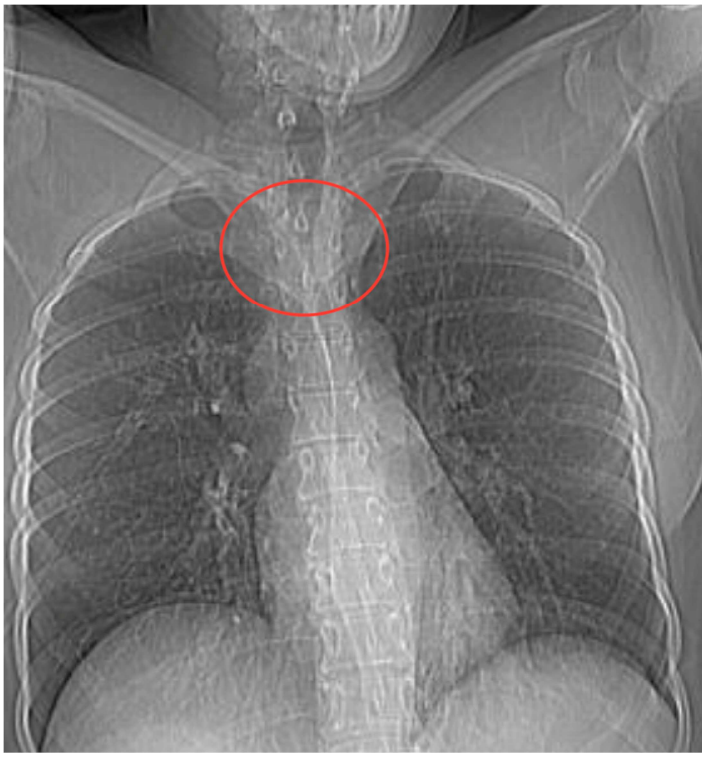

Figure 6. Imaging of tracheal stenosis

ARDS Management

Ventilator Mode

Pressure control until weaning

Tidal volume

Initial <6mL / kg ideal body weight

Driving pressure <15 cm H_2O

Respiratory Rate

With initial change in Vt, adjust RR to maintain minute ventilation

Make subset adjustments to RR to maintain pH 7.3, but do not exceed RR >28-30/min

FiO_2, PEEP and arterial oxygenation

Maintain PaO_2 = 55- 80 mm Hg or SpO_2 = 88-95% using the following PEEP / FiO_2 combinations

FiO_2	0.3-0.4	0.4	0.5	0.6	0.7	>0.8
PEEP	5-8	8-14	8-16	10-20	10-20	14-22

Acidosis Management

If pH < 7.3 increase RR until pH ≥ 7.30 or RR = 35/min

If pH < 7.15, Vt may be increased; consider bicarbonate infusion

Alkalosis management

If pH > 7.45 and patient not triggering ventilator, decrease set RR but not below 6/min

Additional recommendations

Prone positioning ≥ 20 hours per day in severe ARDS

Table 1. ARDS management - Adapted from [19,23].

cm H_2O=Centimetre of water, CPAP= Continuous positive airway pressure; FiO_2= Fraction of inspired oxygen; mm Hg=Millimetre of mercury; paO_2=Arterial oxygen partial pressure; PEEP=Positive end-expiratory pressure; RR=respiratory rate; SpO2= peripheral oxygen saturation; Vt= Tidal volume.

ECMO Indications for patients with ARDS
Indications to start ECMO therapy
Severe hypoxemia: PaO_2/ FiO_2 ratio <50 mm Hg for >3 hours, PaO_2/FiO_2 of <80 mmHg for >6 hours, or Arterial blood pH of <7.25 with $PaCO_2$ of ≥60 mm Hg for >6 hours with the RR increased to 35/min and ventilator settings adjusted to keep a plateau pressure of ≤32 cm H_2O despite ventilator optimization (FiO_2 of ≥0.80, a Vt of 6 ml/kg ideal body weight, and PEEP of ≥10 cm H_2O)

Table 2. ECMO Indications for patients with ARDS. Adapted from [65].

cm H_2O=Centimetre of water, FiO_2= Fraction of inspired oxygen; mm Hg=Millimetre of mercury; paO_2=Arterial oxygen partial pressure; $paCO_2$=arterial carbon dioxide partial pressure; PEEP=Positive end-expiratory pressure; RR=respiratory rate; Vt= Tidal volume.

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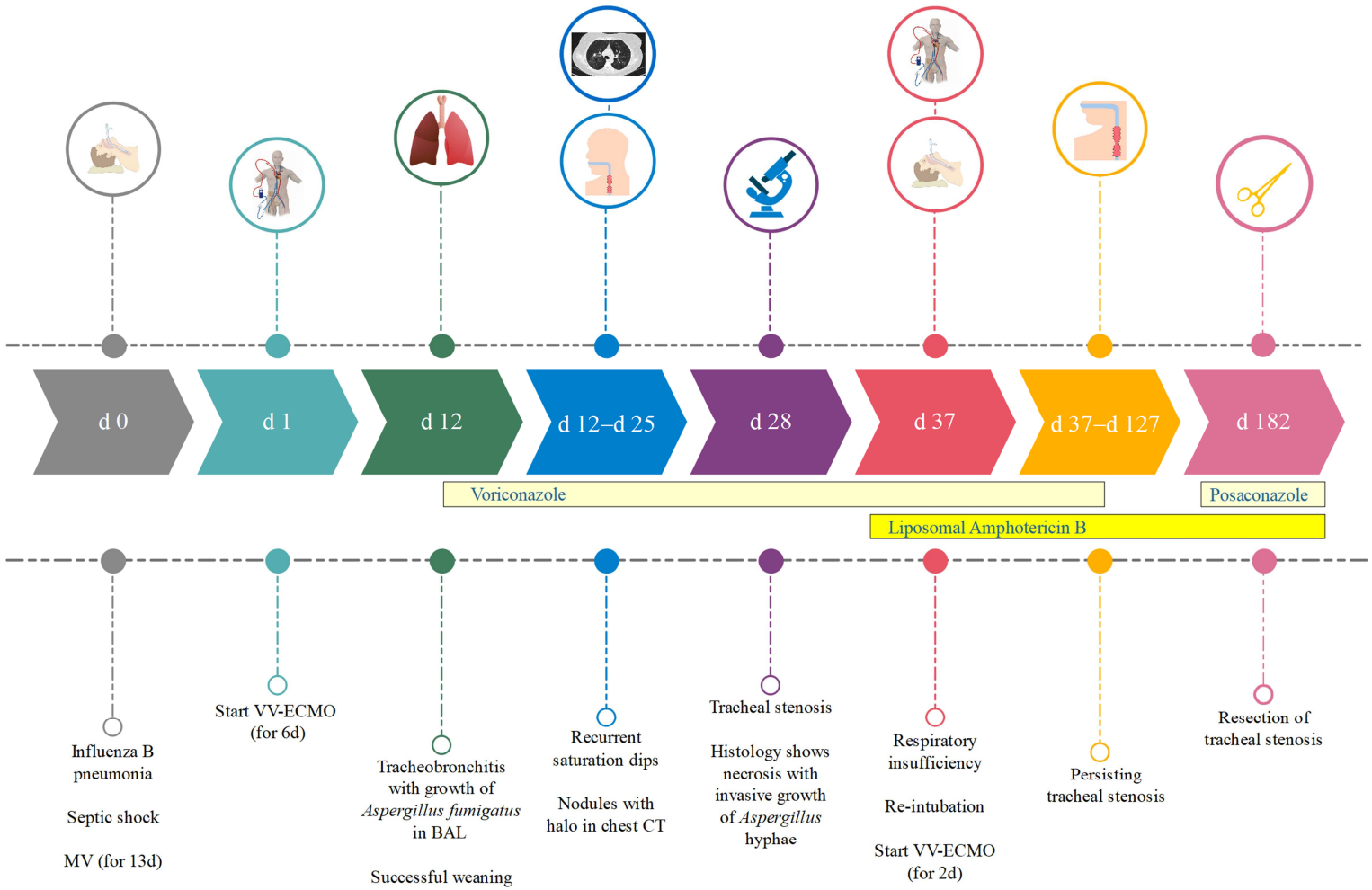

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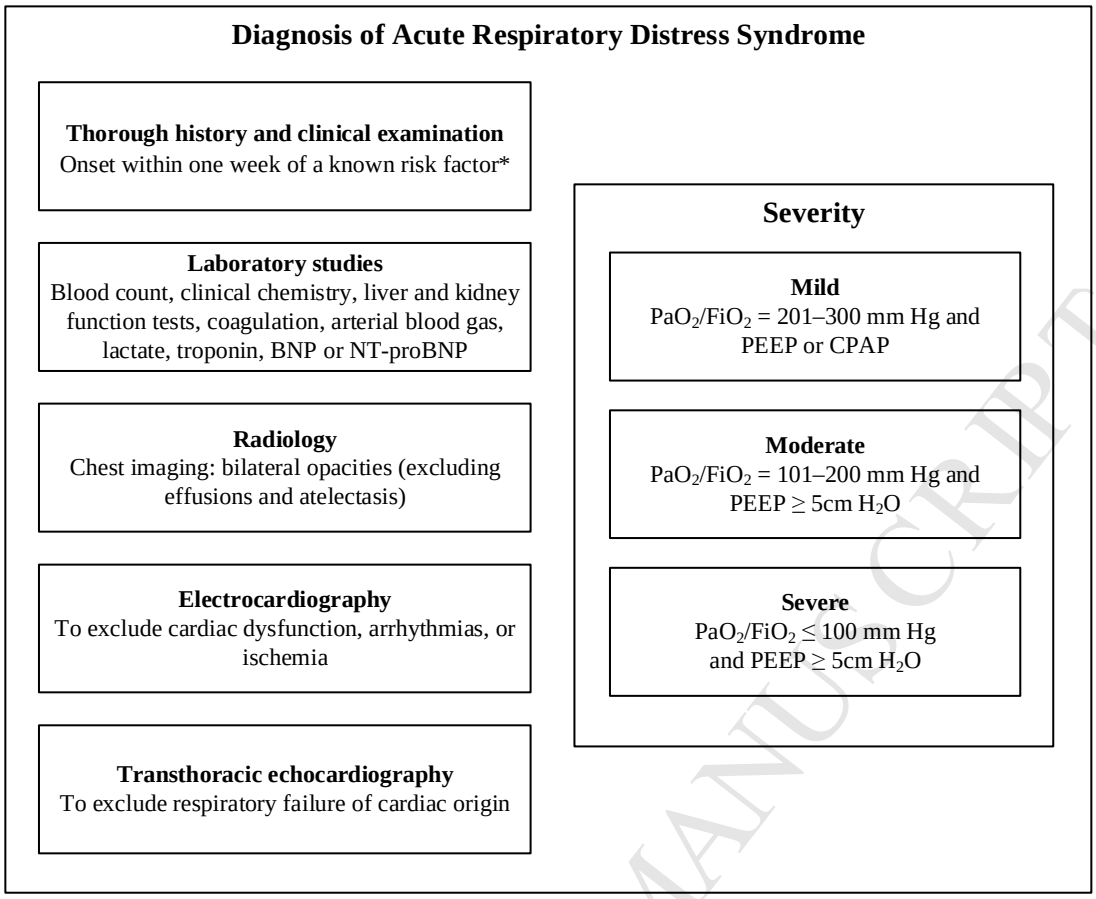

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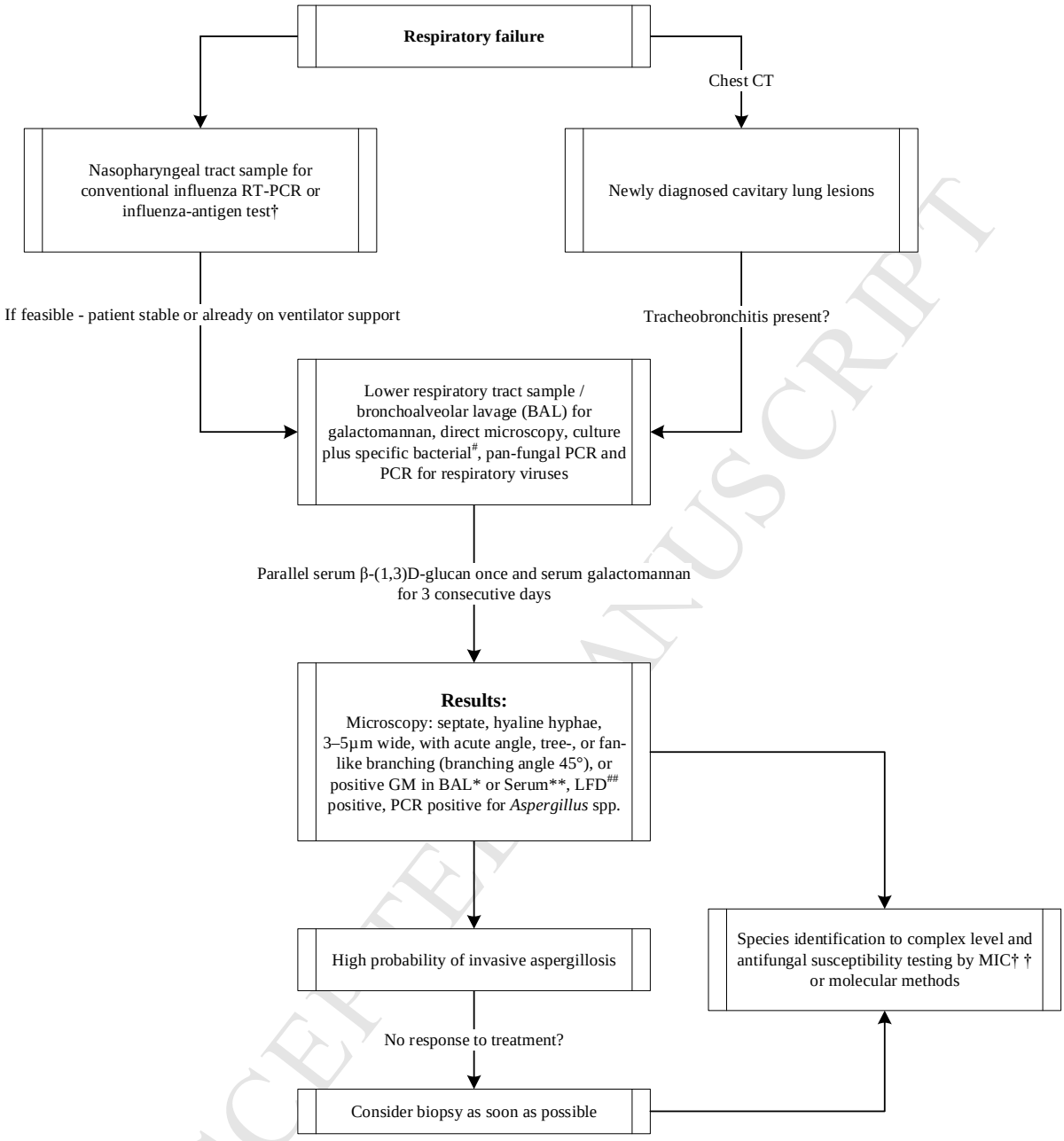

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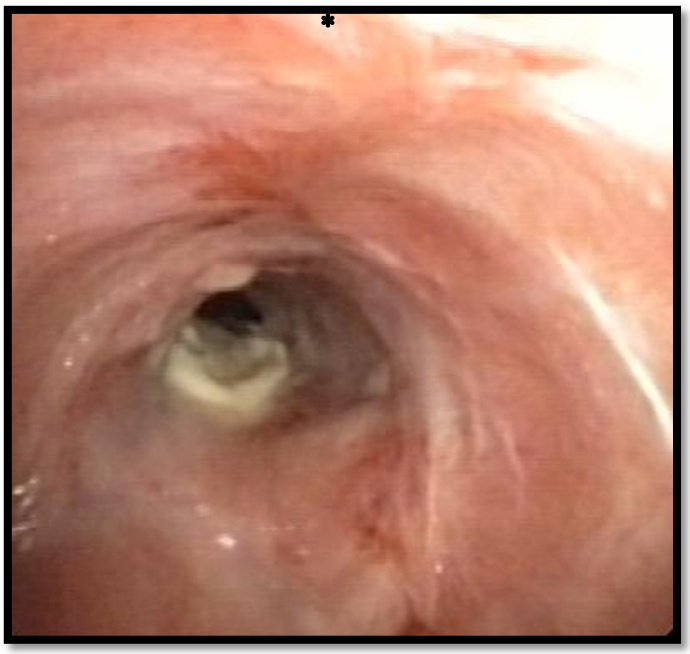

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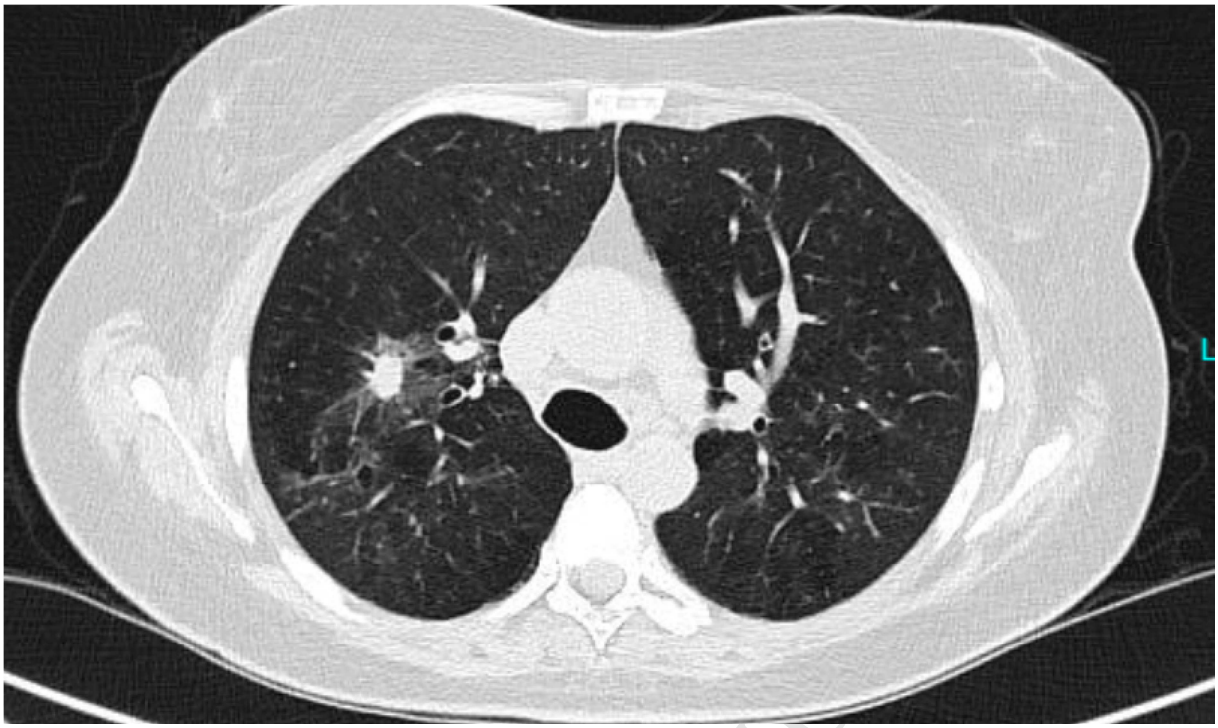

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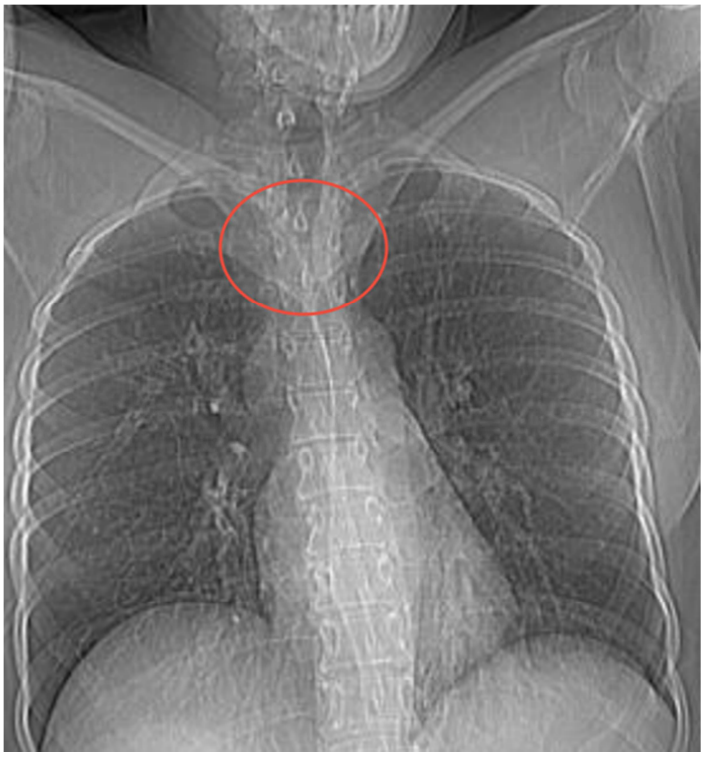

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