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CONNECTIVE TISSUE DISEASE RELATED PULMONARY ARTERIAL HYPERTENSION

Introduction

Pulmonary arterial hypertension (PAH) is increasingly being recognized in patients with connective tissue diseases (CTD), particularly systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD). In fact, a recent analysis of a PAH registry in USA has suggested that 40% of all cases of PAH are associated with CTD. Moreover, the proportion of cases of PAH attributable to CTD has increased over time. Females account for 85% of these patients. CTD associated PAH carries a worse prognosis and greater mortality compared to idiopathic PAH.

Incidence

PAH has been reported in almost every CTD including Sjogren's syndrome, rheumatoid arthritis (RA), antiphospholipid antibody (APLA) syndrome, polymyositis (PM) and dermatomyositis (DM). Incidence of PAH in SSc has been mentioned variably in literature to be as high as 60%. Recent studies using right heart catheterization (RHC) have shown the incidence to be 15-20%. Prevalence of PAH did not differ in patients with diffuse SSc or limited SSc patients, with and without ILD. PAH is seen in 5-14% of all patients with SLE. In SLE, PAH is associated with other- complications including ILD or thromboembolic disease in 50% of cases. Recent studies suggest that 20 - 27.5% of RA have mild PAH when screened with echocardiography.

Pathology and pathogenesis

Pathogenesis and pathology of CTD related PAH is similar in many ways to idiopathic PAH and these have been clubbed into single group 'severe angioproliferative pulmonary hypertension (SAPPH)' by some authors.

The main pathological findings include intimal thickening and hypertrophy of media in small and medium sized vessels. In addition, patients with CTD related PAH also show obliterative changes in venules and preseptal veins, which explains the poor response to pharmacological therapy compared to idiopathic PAH.

Development of intimal thickening can be conceptually divided into two phases. The initial insult appears to be endothelial damage by various antibodies like antiendothelial antibodies and antiphospholipid antibodies. Dysregulated

immunity leads to sustained injury to endothelial cells. This stage is responsive to immunosuppression. In subsequent stages, endothelial cells become apoptosis resistant and cause intimal thickening. This stage is not responsive to immunosuppression.

Vasospasm plays an important role in CTD related PAH. Elevated endothelin levels, endothelial dysfunction, association with Raynaud's phenomenon and reversibility of PAH during right heart catheterization (RHC) lend weight to this argument.

Screening

Despite high incidence PAH remains under diagnosed in patients with CTDs. The UNCOVER study has shown that 13.3% patients with SSc or MCTD followed up in a community rheumatology practice setting have undiagnosed PAH. There are no current guidelines on whom to screen and what the screening modality should be. Moreover, natural history and outcome of treatment (lead time bias) in these asymptomatic patients has not been studied prospectively. Despite these shortcomings, there has been a lot of research in patients with SSc. Various risk factors associated with PAH have been mentioned (box 1). Echocardiographic study of the heart is suggested as a screening tool.

Box 1: Risk factors for PAH in CTDs.

- Symptoms and/or signs of PAH
- Limited SSc of >10 years' duration
- SSc patients with age of onset >60 yrs
- DLCO <50% predicted
- Arapid or large fall in DLCO without evidence of ILD
- Pericardial thickening of 8mm
- Raynaud's phenomenon preceding PAH by 3 yrs
- NT pro-BNP in excess of 395 pg/mL

Evaluation of PAH

All patients diagnosed to have PAH should preferably have an electrocardiogram (ECG), chest radiograph, high resolution computed tomography (HRCT) thorax, Doppler Echo, 6-minute walk test and N terminal pro brain natriuretic peptide (NT-proBNP).

Right heart catheterization helps in accurate diagnosis, assessment of pulmonary hemodynamics and vasodilator response. Patients with CTD related

PAH have reversibility in lesser proportion of patients (3%) compared to those with idiopathic PAH.

N terminal pro BNP

It is an additional biological tool in the evaluation and management of SSc- PAH patients. NT-proBNP cut-off value of 395.34pg/ml had a sensitivity of 69% and specificity of 100% for the diagnosis of PAH in SSc. NT-proBNP values have significantly correlation with pulmonary artery pressures and 6-minute walk distance (6MWD). Serial measurements of NT-pro BNP might be helpful to monitor patients after initiation of treatment and failure of levels to fall might suggest therapeutic failure.

Treatment

Treatment of CTD related PAH is much similar to idiopathic PAH because of similar pathobiology. Apart from supplemental oxygen, diuretics, anticoagulants (with a target of INR 2.0-3.0) and calcium channel blockers, newer prostanoids, endothelin receptor antagonists and sildenafil have been used. Calcium channel blockers like nifedipine, diltiazem have been used in patients with PAH who show significant response to acute vasodilator challenge during right heart catheterization.

Prostanoids like epoprostenol (administered intravenously) and treprostinil (administered subcutaneously) have been studied in CTD related PAH although to a lesser extent than in idiopathic PAH. They have been found to have significant effect both on symptoms, exercise capacity and pulmonary hemodynamics, but no significant mortality benefit. Oral endothelin receptor blocker, bosentan, has shown mortality benefit in addition to symptom relief, improved pulmonary hemodynamics and increased exercise capacity. Newer selective end of the lin-A receptor blockers, ambrisentan and sitaxsentan have not been prospectively studied in CTD related PAH. All these drugs have shown benefit in CTD related PAH in a magnitude similar to that in idiopathic PAH.

In patients with SLE related PAH, immunosuppression with cyclophosphamide and prednisolone has been shown to be effective in small uncontrolled observational studies. However, no long-term studies or recommendations exist.

Balloon atrial septostomy and lung transplant have been offered to those patients in NYHA class 4

despite optimal pharmacotherapy. However, experience in CTD related PAH is limited to few case series and apparently, these patients perform as well as patients with idiopathic PAH do.

Prognosis

In patients with SSc and SLE, presence of PAH signifies poor survival compared to those without PAH. Patients with CTD related PAH have greater mortality rates compared to those with Idiopathic PAH. Poor prognostic markers in these patients are shown in Box 2.

Box 2: Poor prognostic markers

- Advance NYHA functional class.
- Low 6MW distance
- Elevated mean right atrial pressure
- Reduced cardiac index.
- Presence of a pericardial effusion
- Low VO₂ max and low peak exercise systolic and diastolic BP as determined by CPET
- Elevated brain natriuretic peptide (> 180 pg/mL).
- In patients with IPAH treated with epoprostenol, persistence of NYHA class III or IV after 3 months of therapy
- Reduced DLCO (< 45% of predicted)

Summary

PAH in patients with CTDs was previously an under-recognized entity. With better understanding of its prevalence, pathophysiology and availability of multiple therapeutic options, it is important for

clinicians to suspect and screen patients with CTD for PAH. Although various pharmacological agents are available, bosentan is the only drug shown to have an effect on the prognosis of these patients. The overall prognosis of these patients, however, remains poor compared to those with idiopathic PAH.

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EVALUATION AND MANAGEMENT OF RHEUMATOLOGIC EMERGENCIES IN ICU

Rheumatological diseases can present with a wide variety of emergencies. Acute presentations of rheumatological diseases have protean manifestations. It has been shown that upto 20% of patients admitted in emergency medical wards have rheumatological diseases as the cause for admission. Awareness on part of the physician, appropriate investigations and timely treatment are required to assure better outcome in these patients. Various rheumatological emergencies are described here according to organ system involved.

NEUROLOGICAL EMERGENCIES

Meningitis, stroke, seizures and acute onset altered sensorium are life threatening neurological emergencies. A syndrome of fever, head ache and altered sensorium suggesting meningitis warrants lumbar puncture and cerebrospinal fluid (CSF) analysis to differentiate infective bacterial meningitis (neutrophilic pleocytosis, low CSF sugar, Gram stain or culture positivity) from aseptic meningitis (lymphocytic pleocytosis, normal sugar and

negative microbiological studies). Bacterial meningitis in these patients warrants additional ampicillin to cover *Listeria monocytogenes*. Aseptic meningitis due to systemic lupus erythematosus (SLE) and vasculitides is treated with high dose steroids. Non steroidal anti inflammatory drugs (NSAIDS) and intravenous immunoglobulin G (IVIG) that are often used for treating rheumatic diseases are known to cause aseptic meningitis which responds to withdrawal of the offending drug.

Stroke in the presence of rheumatic disease needs to be investigated for bland infarct due to vascular occlusion and vasculitic infarct. Bland infarct may be due to atheroembolism, embolism from Libman-Sack's endocarditis or in-situ thrombosis secondary to antiphospholipid antibody (APLA) syndrome. Central nervous system (CNS) imaging, carotid Doppler, echocardiography, lupus anticoagulant (LAC) and anticardiolipin antibody (aCL) complete the work-up. Infarct due to APLA requires lifelong anticoagulation, whereas atheroembolism is treated with high dose steroids in addition to anticoagulation.

In patient with acute onset diffuse CNS dysfunction, diffuse vasculitis [SLE, polyarteritis nodosa (PAN), Wegner's granulomatosis and isolated CNS angiitis] should be differentiated from diffuse vascular occlusion due to APLA. MRI, cerebral angiogram and brain/leptomeningeal biopsy differentiates the two. CNS vasculitis mandates immunosuppression where as vascular occlusion is treated with therapeutic anticoagulation.

Other causes of acute altered sensorium like seizures (SLE, APLA), accelerated hypertension, scleroderma renal crisis (SRC) and thrombotic thrombocytopenic purpura (TTP) should be considered according to the clinical picture.

HEMATOLOGICAL EMERGENCIES

Severe autoimmune cytopenias (anemia and thrombocytopenia) can complicate SLE. High dose steroids, IVIG and splenectomy in refractory conditions have been the mainstay of therapy for years. IVIG, although used, is shown to have no additional benefit in patients with thrombocytopenia, when added to high dose steroids and its utility in anemia is not clear. Recently Rituximab (monoclonal anti CD-20 antibody) has been used with success in these patients.

Clinical course of SLE may be punctuated with TTP. Clinical manifestations, investigations and

management do not differ from other cases of TTP. Daily plasma exchange till the platelet counts are stable above 50,000/uL is recommended as the first line therapy with addition of high dose steroids in unresponsive cases.

CARDIAC EMERGENCIES

Coronary ischemia in the presence of rheumatological disorder might be due to atherosclerosis (RA, SLE are known to accelerate atherosclerosis), arteritis (as seen in PAN, Churg Strauss syndrome [CSS] and Takayasu's arteritis) or due to thrombosis secondary to APLA. In addition to standard management of acute coronary syndrome, vasculitides require immunosuppression. Revascularization in Takayasu's arteritis is attempted after disease activity is controlled.

Myocarditis amounting to congestive heart failure (CHF) and pericardial effusion leading to tamponade occur rarely in SLE and high dose steroids in addition to standard management is the mainstay of therapy. Steroid resistant myocarditis have been treated with IVIG and cyclophosphamide.

PULMONARY EMERGENCIES

APLA is associated with pulmonary embolism (PTE) and there is a strong association between LAC and PTE in case controlled studies. Patients with APLA have a 8% risk of thrombotic events over a 5 year follow up. Management of acute PTE is not different from those with out APLA. However, patients with APLA who develop PTE should be on life long oral anticoagulation.

Diffuse parenchymal lung disease (DPLD) with acute hypoxic respiratory failure (AHRF) in the setting of rheumatic disease has a varied etiology and necessitates bronchoscopy with bronchoalveolar lavage (BAL) for differentiation. Lung biopsy (bronchoscopic or open) would further help to differentiate these conditions (Table1).

Table 1 : Differentiation of DPLD

	Clinical features	Radiological features	BAL	Lung biopsy
Pneumonia	AHRF	Multilobar consolidation	Microbiological stains and Culture +	
Lupus pneumonitis	AHRF	Multilobar consolidation (lower lobes)		•DAD, NSIP •Org. pneum. •Capillaritis
DAH	•AHRF •Hemoptysis •Fall in Hb	Multilobar consolidation MRI:↑ signal in T2W image	•Hemorrhagic •Hemosiderin laden macroph.	•Capillaritis +/- •Hemosiderin macrophages
MTX induced DPLD	•h/o MTX	Diffuse interstitial pattern	Lymphocytosis High CD4:CD8	Desquamative lesions

Lupus pneumonitis is seen in 2-4% of patients with SLE, but it is the presenting manifestation in 50% of them. Histological picture shows predominant diffuse alveolar damage (DAD). High dose steroids with cover of broad spectrum antibiotics are the mainstay of treatment. Steroid resistant cases might respond to CYC, IVIG, plasmapheresis or Rituximab. Mortality rates are as high as 50% once respiratory failure sets in. Methotrexate induced DPLD can present acutely. Withdrawal of methotrexate with institution of steroids assures recovery in most of the patients.

Diffuse alveolar hemorrhage (DAH) presents with triad of DPLD, hemoptysis and fall in hematocrit value. Differentiation of various etiologies of DAH and pulmonary renal syndromes is shown in table 2. High dose steroids and CYC are the mainstay in ANCA associated vasculitides and SLE, whereas, in Goodpasture's syndrome, early plasmapheresis till the antibody titres go undetectable gives good outcome. In cases where the etiology is not clear, plasmapheresis should be offered till Goodpasture's syndrome is ruled out. Use of plasmapheresis in SLE, although tried in cases with resistant DAH, does not have survival benefit, where as it has been shown to have utility in ANCA associated vasculitides. IVIG and Rituximab have been used sparsely with good results in refractory cases of SLE and vasculitides.

Table 2 : Differentiating features of DAH and pulmonary renal syndromes

Table 2: Differentiation various etiologies of DAH, RPGN

Disease	DAH / RPGN	Arthritis	S kin vasculitis	ANA	Cl	Immun. markers	Tissue Ab. Staining
Wegner's granulomatosis	DAH+ RPGN	+	+	±	N	C-ANCA	-
Microscopic polyangitis	DAH+ RPGN	+	+	±	N	P-ANCA	-
Goodpasture's syndrome	DAH+ RPGN	-	-	-	N	Anti-GBM	Linear
SLE	DAH+ RPGN	+	±	+		Anti ds-DNA	Granular
Renal limited crescentic GN	RPGN	-	-	-	N	P-ANCA	-
Cryoglobulinemia	RPGN	+	+	-		Cryocrit Anti HCV	Granular
Anti GBM dis.	RPGN	-	-	-	N	Anti-GBM	Linear
Isolated pulmonary capillaritis	DAH	-	-	-	N	-	

RENAL EMERGENCIES

Rheumatic diseases can present as rapidly progressive glomerulonephritis (RPGN). Differentiation

of various etiologies presenting as RPGN is given in table 2. Similar to DAH, all of the conditions except Goodpasture's syndrome are treated with high dose steroids and CYC. Hepatitis C virus (HCV) associated cryoglobulinemia is treated with interferon and ribavirin in addition to immunosuppression. Plasmapheresis has been successfully used in cases of Wegner's granulomatosis with severe RPGN requiring dialytic support with good results. Current recommendations suggest creatinine value of 6mg/dl as cut-off. Rituximab has been extensively used in cases of cryoglobulinemia refractory to standard management.

Scleroderma renal crisis presenting as accelerated hypertension with rapidly progressive renal failure (RPRF) is seen in upto 10% of cases of systemic sclerosis. Risk factors include diffuse scleroderma, early disease, use of high dose (>40mg/day) steroids and renal hypoperfusion (sepsis, dehydration, drugs decreasing renal perfusion). Laboratory abnormalities include mild azotemia, microscopic hematuria, proteinuria, granular casts, hemolytic anemia and thrombocytopenia (rarely below 50,000/uL). Treatment with ACE inhibitors such as captopril to control blood pressure to 120/80 mm Hg is the treatment of choice. In pre-captopril era <10% of patients survived the 1st year, where as current 5 year survival rates are around 65%.

GASTROINTESTINAL EMERGENCIES

Rheumatic diseases can present as acute mesenteric vein thrombosis (APLA) and mesenteric arteritis (PAN, CSS, Wegner's granulomatosis). Mesenteric arteritis can have varied clinical presentation (acute abdomen with bloody diarrhea, bowel infarction, GI bleed, bowel perforation, cholecystitis, pancreatitis, appendicitis). Treatment for mesenteric arteritis is with steroids and cyclophosphamide as dictated by the etiology.

CATASTROPHIC APLA

This is truly a rheumatological emergency, seen in 1% of cases with APLA. Presentation is with recurrent arterial thromboses involving multiple sites (stroke; cardiac, hepatic, renal, adrenal and/or intestinal infarction and peripheral gangrene) over a short duration of time. Occurrence of >3 thrombotic events in 7 days duration in proven or suspected case of APLA might be indicative of catastrophic APLA. Differential diagnosis includes disseminated intravascular coagulation (DIC) and TTP. Investigations generally show a positive aPL

and/or LAC (which are not seen in other mimics), thrombocytopenia is usually present along with normal RBCs on peripheral smear (differentiates from TTP) and fibrin degradation products (FDP) is not elevated (differentiates from DIC). A multipronged approach with therapeutic anticoagulation, high dose steroids and IVIG or plasmapheresis has been shown to have good results with 70% recovery rates.

SUMMARY

Rheumatic diseases can present with protean manifestation involving any organ system. A high index of suspicion in a given clinical setting and appropriate investigations may help in early diagnosis. With current therapeutic modalities (immunosuppression, plasmapheresis, IVIG), good results may be obtained if initiated in time. Newer therapeutic modalities like Rituximab are being explored as salvage therapy in various clinical settings with good results.

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JOURNAL CLUB CRITIQUE

Heyland DK, Dodek P, Muscedere J, et al for the Canadian Critical Care Trials Group. **Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator associated pneumonia.** *Crit Care Med* 2008; 36: 737–744.

ABSTRACT

Objective

To compare a strategy of combination therapy with a strategy of monotherapy with broad-spectrum antibiotics for suspected late ventilator-associated pneumonia.

Design

Randomized trial

Setting

Twenty-eight intensive care units in Canada and the United States

Patients

The study included 740 mechanically ventilated patients who developed suspected ventilator-associated pneumonia after 96 hrs in the intensive care unit. Patients known to be colonized or infected with *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* or who were immunocompromised were excluded from the study.

Interventions

As initial unblinded therapy, patients were allocated to receive meropenem (1 g every 8 hrs) and ciprofloxacin (400 mg every 12 hrs) or meropenem alone. Before starting antibiotics, patients were also randomized to bronchoalveolar lavage with quantitative cultures or endotracheal aspirates. When culture results were available, physicians were encouraged to adjust antibiotics. Adequacy of antibiotics was defined as the organism present in the enrollment culture having in vitro susceptibility to one or more of the study antibiotics.

Measurements and Main Results

Baseline characteristics and etiologies of ventilator-associated pneumonia were similar in the two groups. There was no difference in 28-day mortality between the combination and monotherapy groups (relative risk = 1.05, 95% confidence interval 0.78 –1.42, p = 0.74). Duration of intensive care unit and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool, and fungal colonization were also similar in the two groups. In a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacilli at enrollment (n = 56),

the adequacy of initial antibiotics (84.2% vs. 18.8%, $p < 0.001$) and microbiological eradication of infecting organisms (64.1% vs. 29.4%, $p = 0.05$) was higher in the combination group compared with the monotherapy group, but there were no differences in clinical outcomes.

Conclusions

For critically ill patients who have suspected late ventilator-associated pneumonia and who are at low risk for difficult-to-treat Gram-negative bacteria, monotherapy is associated with similar outcomes compared with combination therapy. For those patients at high risk of difficult-to-treat Gram-negative bacteria, combination therapy is safe and may be associated with better microbiological and clinical outcomes.

COMMENT

Empirical combination therapy with broad spectrum antibacterials for suspected late onset ventilator-associated pneumonia (VAP) remains a controversial issue. Since a delay in the initiation of treatment with appropriate antibiotics is an independently risk factor for mortality related to VAP, available guidelines for the management of VAP recommend its prompt initiation. However, there is no consensus on the choice of agent(s) to be used since it is believed that this decision should be guided by the current trends of pathogens and their susceptibility patterns at a given ICU. Similarly, most guidelines advocate that in patients with late-onset VAP or early onset VAP with risk factors for infection with multi-drug resistant pathogens, treatment with combination broad-spectrum antibacterial drugs should be initiated promptly and de-escalation attempted after culture results become available. It has been reasoned that use of combination therapy would lead to synergy and prevent the emergence of resistance during treatment. However, available data does not support the same.

Dr. Mical Paul and colleagues in 2004 published a meta-analysis of 64 randomized trials that had compared β -lactam monotherapy with β -lactam-aminoglycoside combination therapy and involved 7586 non-neutropenic patients with sepsis including almost 1200 with VAP. In this meta-analysis, they showed that patients who had been treated with combination therapy had similar all-cause mortality rates as those treated with monotherapy. The same results were seen in subgroups of patients with infections by Gram negative bacteria ($n = 1835$) and *Pseudomonas aeruginosa* ($n = 426$). On the other hand, nephrotoxicity was more common in patients treated with aminoglycosides.

There was no difference among the two groups with respect to rates of development of antibiotic resistance.

If one considers the issue of drug resistance, combinations involving the use of fluoroquinolones have led to worse outcomes than those without. It has been reported that methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum-lactamase (ESBL) producing Gram-negative bacilli are isolated more frequently from patients treated with fluoroquinolones compared with those not treated with this class of antibacterial agents. It is therefore not surprising to know that the incidence of ciprofloxacin resistance among *Pseudomonas aeruginosa* and other Gram-negative bacilli has doubled in the last decade. Moreover, use of fluoroquinolones is associated with the risk of increasing resistance to carbapenems by inducing efflux pump systems. An additional risk with the indiscriminate use of fluoroquinolones in India and other countries that have high prevalence rates of tuberculosis is the masking and promotion of fluoroquinolones resistance among *Mycobacterium tuberculosis* isolates. This is particularly so where tuberculosis has not been or cannot be completely excluded prior to initiation of drug therapy.

The current study by Dr. Daren Heyland and colleagues compared meropenem monotherapy with a combination therapy (meropenem plus ciprofloxacin) as initial treatment for suspected late-onset VAP. They reported similar outcomes in the two groups in terms of 28 day mortality, duration of ICU and hospital stay, treatment response and emergence of antibiotic-resistant bacteria. Patients who were known to be previously colonized or infected with *P. aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA) or who were immunocompromised were excluded from the study. Ironically, these are the very patients in whom monotherapy may be theoretically more likely to result in treatment failure. In fact, subgroup analysis of patients who after enrollment were detected to have infections due to *Pseudomonas* spp., *Acinetobacter* spp., and multidrug-resistant Gram-negative bacilli, adequacy of initial antibiotics (84.2% vs. 18.8%, $p < 0.001$) and microbiological eradication (64.1% vs. 29.4%, $p = 0.05$) was better in the combination therapy group. These findings lend support to the widely prevalent consensus opinion regarding the use of an initial double drug combination for suspected *Pseudomonas* spp. infection.

IMPLICATIONS FOR DAY-TO-DAY PRACTICE

In critically ill patients with suspected late onset VAP and who are at low risk for infection by *Pseudomonas*

spp., *Acinetobacter* spp., and other multi-drug resistant Gram-negative bacteria, monotherapy with a broad spectrum β -lactam antibiotic should be initiated since combination therapy is unlikely to provide additional benefit in any of the outcome parameters and may in fact be associated with an increased risk of adverse effects (aminoglycosides) and emergence of drug resistance (fluoroquinolones). On the other hand, patients in whom there is indeed a high risk of infection by the above mentioned bacteria (see Table 1), combination therapy (preferably of a β -lactam with an aminoglycoside) should be preferred since it can lead to better outcomes. De-escalation and switching to monotherapy is feasible and safe and should be attempted once reports of culture and susceptibility are available.

Table 1: Risk factors for infection with multi drug resistant bacterial pathogens

<ul style="list-style-type: none"> • Hospitalization for ≥ 48 hours in the last 30 days • Broad spectrum antibiotic therapy for ≥ 7 days in the preceding 30 days <ul style="list-style-type: none"> ➢ Second/third generation cephalosporins ➢ Aminoglycosides or fluoroquinolones) • Patients of chronic renal failure on maintenance hemodialysis • Immunosuppressive therapy including glucocorticoid therapy • Neutropenia • Severe protein energy malnutrition (BMI < 16) • Severe structural lung disease <ul style="list-style-type: none"> ➢ Bronchiectasis (FEV1 < 30%) ➢ COPD (FEV1 < 30%) ➢ ILD (FVC < 30%)]
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