Pharmacologic Treatment for Bronchiectasis

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16:00-16:40, 3 Aug., 2019

BTS Guideline for bronchiectasis in adults. Thorax 2019;74(Suppl 1):1-69

Bronchiectasis: case 1

Patient characteristics:

- Chen, 77 yr female, never smoker, occupation = NS, sinusitis (-), AR (-), GERD (-), PND(-)
- PH = DU + HP infection s/p eradication in 2011, glaucoma in 2015, NTM in 2018, hernia s/p surgery
- CM OPD (2019/5/15) = purulent sputum, s/p Augmentin, flumucil, xanthium
- CM OPD (2019/5/22) = flumucil, xanthium
  - C3, C4, IgG (H), IgA (H), IgM, IgG4 (H 215.2), RF (-), c/p-ANCA (-), SSA/SSB (-), ANA (80), anti-dsDNA (-)
  - Sialoscintigraphy: class III (severe dysfunction)
  - Total IgE = 136 , Eos count = 78/cumm, ESR = 70mm/hr, CRP = 6.67 mg/dl, ECP 17.4 ug/L
  - PFT (FVL and Lung volume), CXR
- CM OPD (2019/6/19) = flumucil, xanthium, Duasma, prednisolone 5mg bid, eurodin

2019/5/30

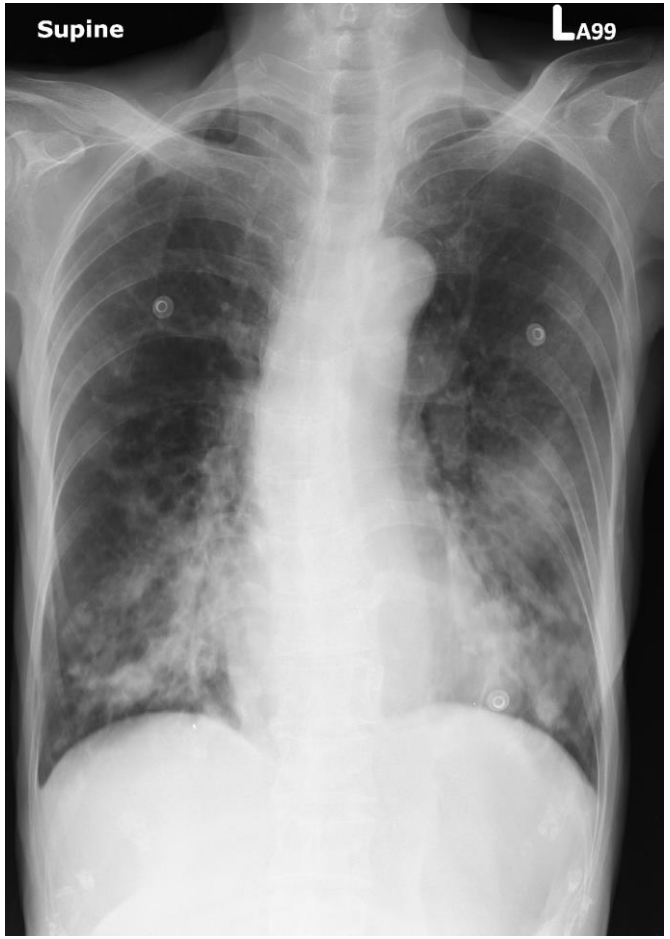
AGE:(77) SEX:( ) HEIGHT:(150) WEIGHT:(29)

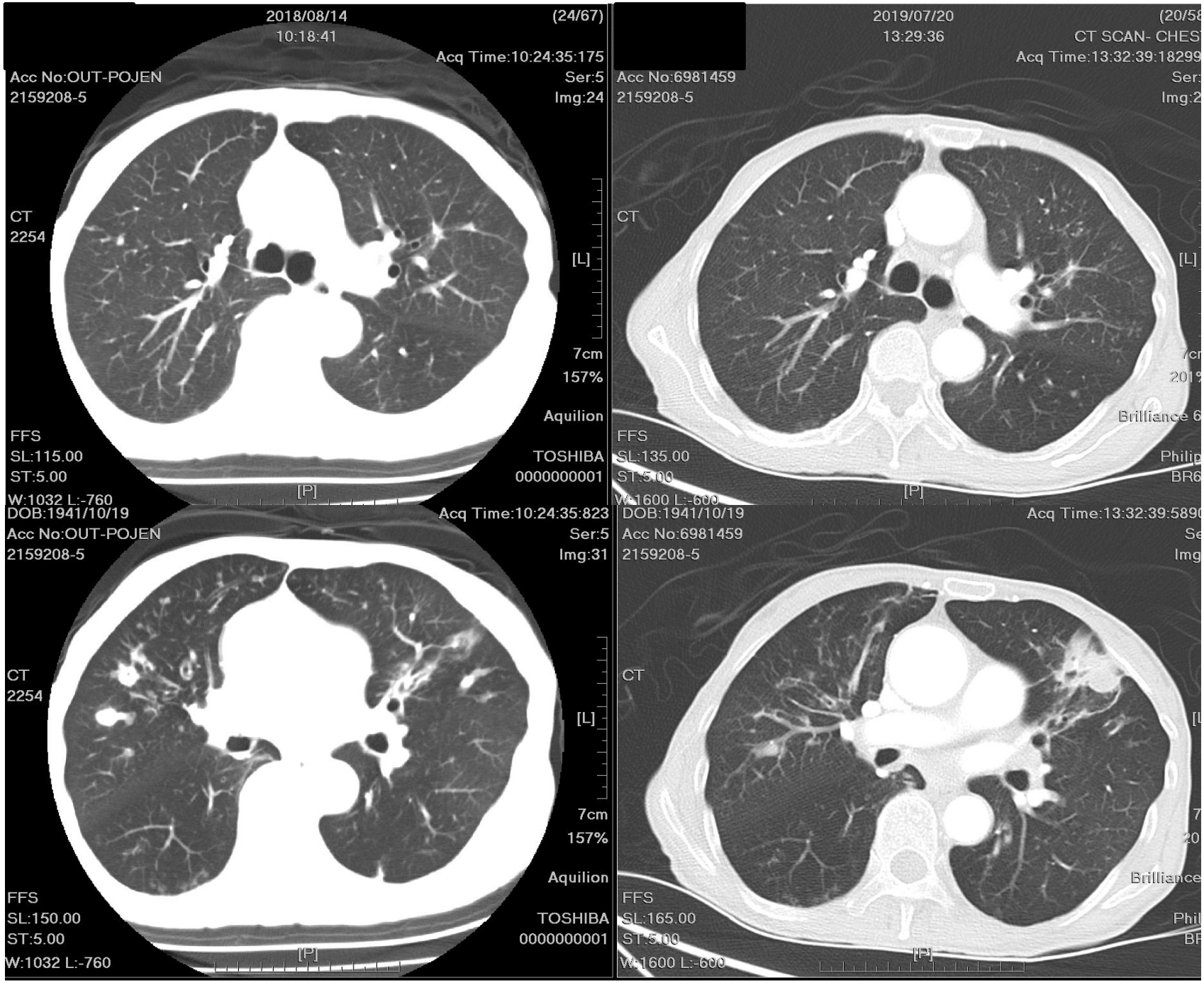
SPIROMETRY		PRED	ACTUAL		%PRED
FVC	LITERS	2.17	1.05	*	48
FEV1	LITERS	1.62	0.79	*	49
FEV1/FVC	%	74	75		101
FEF25-75%	L/SEC	2.18	0.61		28
FEF25%	L/SEC	4.86	2.04	*	42
FEF50%	L/SEC	2.75	0.81	*	30
FEF75%	L/SEC	0.26	0.23		86
FEF200-1200	L/SEC	3.92	0.14	*	4
PEF	L/SEC	5.32	2.04	*	38
PEF/FEV1	UNITLESS	3.28	2.58	*	78
E CODE			1		
LUNG VOLUMES					
VC	LITERS	2.17	1.05	*	48
TLC	LITERS	3.9	2.65	*	68
RV	LITERS	1.73	1.6		93
RV/TLC	%	44	60		136
FRC	LITERS	2.54	1.9	*	75
FRC/TLC	%	0.65	0.72		90
ERV	LITERS	0.64	0.3	*	47
IC	LITERS	1.53	0.75	*	49
AIRWAY RESISTANCE					

- **Hospitalization (2019/7/20-7/30)**

- hemoptysis 100-200ml and dyspnea, no wheezing but rhonchi, rales
- CXR/Chest CT (2019/7/20)
- Acid fast stain (7/24) = 2+, 1+, TB-PCR (-), Sputum culture (7/23) = OSSA, 3 atypical pathogen (-)
- Blood: elevated CA -125 (48.8) and CYFRA 21-1 (3.02), CrAg LFA (-), galactomann Ag (-)
- Lab (7/20): wbc 11600, Hb 11.6,PTL 356k, S/L 95/4%, Eos 0%, CRP = 1.66 mg/dl, d-dimer =0.218 (<0.5 ug/l)
- Antibitoic = Tazocin + Teicoplanin
- Combivent 1 vial UDV q6hv
- prednisolone 5mg qd

2019/7/20

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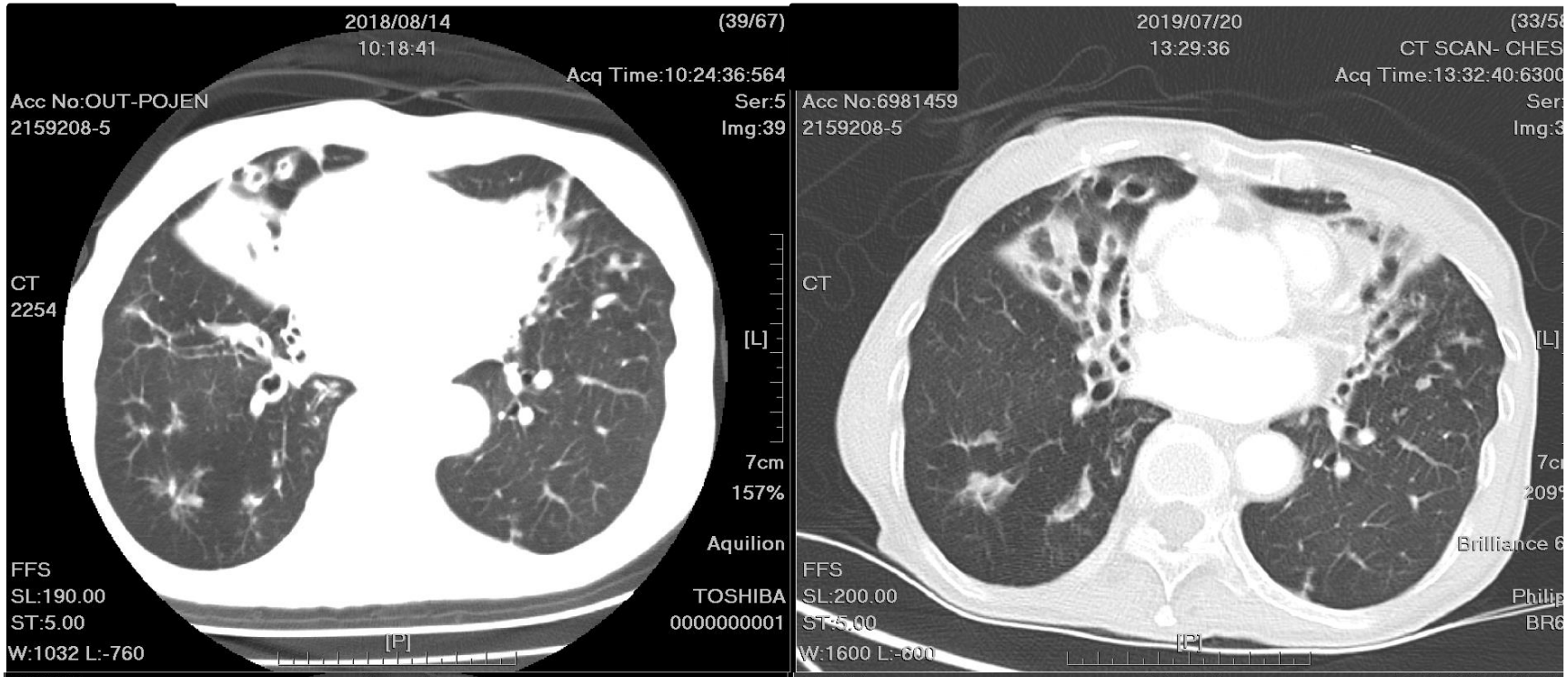
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The DETERIORATING BRONCHIECTATIC PATIENTS

symptoms↑, exacerbation↑, hospitalization↑, PFT↓

ASSESSMENT

1. Ensure patient understanding
2. Assess dx progression
   - ABG
   - Spirometry, lung volume, DLco
   - CT
3. Reassess pathogen
   - S/C for bacteria, fungi
   - Mycobacterial culture
4. Underlying causes
5. Comorbidities
   - Echocardiogram (LV, pul HTN)
   - Sinus disease
   - Exclude PE

OPTIMIZATION

FURTHER MANAGEMENT

The DETERIORATING BRONCHIECTATIC PATIENTS

symptoms↑, exacerbation↑, hospitalization↑, PFT↓

ASSESSMENT

1. Ensure patient understanding
2. Assess dx progression
3. Reassess pathogen
4. Underlying causes
5. comorbidities

OPTIMIZATION

1. Airway clearance
   - Check compliance
   - Physiotherapy +/- PR
   - Consider muco-active treatment
2. Exacerbation
   - Appropriate antibiotic
   - Correct antibiotic duration
   - Check not meeting the requirement for IV antibiotic therapy

3. Oxygen

FURTHER MANAGEMENT

Muco-Active Treatment

- **Mucolytic:**
  - Recombinant human Dnase (Dnase, dornase alpha, pulmozyme): DO NOT routinely use (A)
  - Bromhexine hydrochloride
  - Carbocysteine: a 6-month trial, ongoing if having clinical benefit
- **Mucokinetics**/expectorants (facilitate cough transportability)
  - Humidification with normal/isotonic saline (D)
  - Hypertonic saline (≥3%NaCL)
  - Mannitol (340mg over 12wks, 400mg over 12 months)
  - Pre-treatment with a bronchodilator prior to inhaled/nebulized mucoactive treatment (e.g. asthma, hyper-reactivity, FEV1 <1 L)
- **Mucoregulators**
  - Erdosteine (Erdotin, scavenging activity of free radicals)

Antibiotic for AE-Bronchiectasis

Table 6 Common organisms associated with acute exacerbation of bronchiectasis and suggested antimicrobial agents- adults

Organism	Recommended first line treatment	Length of treatment	Recommended second line treatment	Length of treatment
Streptococcus pneumoniae	Amoxicillin 500 mg Three times a day	14 days	Doxycycline 100 mg BD	14 days
Haemophilus influenzae- beta lactamase negative	Amoxicillin 500 mg Three times a day Or Amoxicillin 1G Three times a day Or Amoxicillin 3G BD	14 days	Doxycycline 100 mg BD Or Ciprofloxacin 500 mg or 750 mg BD Or Ceftriaxone 2G OD (IV)	14 days
Haemophilus influenzae- beta lactamase positive	Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days	Doxycycline 100 mg bd Or Ciprofloxacin 500 mg or 750 mg BD Or Ceftriaxone 2G OD (IV)	14 days
Moraxella catarrhalis	Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days	Clarithromycin 500 mg BD Or Doxycycline 100 mg BD Or Ciprofloxacin 500 mg or 750 mg BD	14 days

2nd : FQ (cipro, levofloxacin, moxifloxacin, nemonoxacin), Macrolide, ceftriaxone iv.

Table 6 Common organisms associated with acute exacerbation of bronchiectasis and suggested antimicrobial agents- adults

Organism	Recommended first line treatment	Length of treatment	Recommended second line treatment	Length of treatment
Staphylococcus aureus (MSSA)	Flucloxacillin 500 mg Four times a day	14 days	Clarithromycin 500 mg BD Or Doxycycline 100 mg BD Or Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days
Staphylococcus aureus (MRSA) Oral preparations	Doxycycline 100 mg BD Rifampicin (<50 Kg) 450 mg OD Rifampicin (>50 Kg) 600 mg OD Trimethoprim 200 mg BD	14 days	Third line Linezolid 600 mg BD	14 days
Staphylococcus aureus (MRSA) Intravenous preparations	Vancomycin 1 gm BD* (monitor serum levels and adjust dose accordingly) or Teicoplanin 400 mg OD	14 days	Linezolid 600 mg BD	14 days
Coliforms for example, Klebsiella, enterobacter	Oral Ciprofloxacin 500 mg or 750 mg BD	14 days	Intravenous Ceftriaxone	14 days

Table 6 Common organisms associated with acute exacerbation of bronchiectasis and suggested antimicrobial agents- adults

Organism	Recommended first line treatment	Length of treatment	Recommended second line treatment	Length of treatment
Pseudomonas aeruginosa	Oral Ciprofloxacin 500 mg bd (750 mg bd in more severe infections)	14 days	**Monotherapy:** Intravenous Ceftazidime 2G TDS or Piperacillin with tazobactam 4.5G TDS or Aztreonam 2G TDS or Meropenem 2G TDS **Combination therapy** The above can be combined with gentamicin or tobramycin or Colistin 2MU TDS (under 60 kg, 50 000–75 000 Units/kg daily in 3 divided doses) Patients can have an *in vivo* response despite in vitro resistance. Caution with aminoglycosides as highlighted below but also if previous adverse events, particularly previous ototoxicity/acute kidney injury due to aminoglycosides	14 days

Anti-Inflammatory Therapies

- **Inhaled corticosteroid:**
  - DO NOT routinely use without other indications (ABPA, chronic asthma, COPD, inflammatory bowel disease)(B)
  - Reduction of sputum volume [Elborn JS 1992, Martinez-Garcia MA 2006], not a significant improvement of FEV1 and FVC, no reduction in AE [Kapur N 2009]
- **Oral corticosteroid:**
  - DO NOT routinely use without other indications (ABPA, chronic asthma, COPD, inflammatory bowel disease)(D)
- **PDE4 inhibitor, xanthium, leukotriene receptor antagonist**
  - DO NOT routinely use(D)
  - No RCT

- **CXCR2 antagonist, neutrophil elastase inhibitor, statins**
  - DO NOT routinely use(D)
  - A reduction in sputum neutrophil count in **CXCR2 antagonist** (AZD5069) tx for 28 days (n= 52), no significant difference in exacerbation. [De Soyza A 2015]
  - No difference in sputum neutrophils but an improvement of 100ml in FEV1 in **NE inhibitor** group (n = 38, 4wks tx) [RCT, Stockley R 2013]
  - A reduction of cough in **Atorvastatin** 80mg qd for 6 months (n=30) vs placebo [Mandal P 2014]
  - Not improve cough in atorvastatin 80mg qd for 3 months, but significant improvement in SGRQ in chronic infected *P. aeruginosa*.[Bedip P 2017]

Bronchodilator Therapies

- **Long acting beta-2-agonist:**
  - Airflow obstruction in ≥60% of bronchiectasis pt with symptoms of breathlessness [Chalmers JD 2014]
  - Improve health related quality of life in BUD/FOR (n=40) vs. BUD [Goyal V 2014]
- **Long acting anticholinergic agents** (No RCT)
  - Reversibility to LAMA is not a requirement for benefit [Nogtady SG 1978]
- **Short acting bronchodilators** (No RCT)
  - Data from COPD and asthma suggests an acceptable safety profile.
- **Evidence statement**
  - Offer a trial of LABA or use of bronchodilator in patient with bronchiectasis and co-existing COPD/asthma (D)
  - Reversibility testing may help to identify asthma but no evidence to suggest benefit from treatment (D)

The DETERIORATING BRONCHIECTATIC PATIENTS

symptoms↑, exacerbation↑, hospitalization↑, PFT↓

ASSESSMENT

1. Ensure patient understanding
2. Assess dx progression
3. Reassess pathogen
4. Underlying causes
5. comorbidities

OPTIMIZATION

1. Airway clearance
2. Exacerbation
3. Oxygen

FURTHER MANAGEMENT

- Treat identified cause
- Treat associated comorbidities
- Consider iv. antibiotic
- Consider if needed
  - LTOT +/- NIV
  - Surgery
  - Transplantation
  - End of life support

Stepwise Management

Step 1	Step 2	Step 3
	≥3 exacerbation despite step 1*	≥3 exacerbation despite step 2*
• Treat underlying cause • Airway clearance +/- PR • Influenza vaccination • Antibiotic for exacerbation • Self management plan	• Physiotherapy reassessment • Muco-active treatment	• If P. aeruginosa: long term inhaled anti-PA antibiotic or macrolide • If other pathogen: long term macrolide or oral/inhaled targeted antibiotic • If no pathogen: long term macrolides

*consider this step if significant symptoms persistent despite previous step
Exacerbation = acute deterioration (several days) with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, hemoptysis) and/or systemic upset

Step 4	Step 5
≥3 exacerbation despite step 3*	≥3 exacerbation despite step 4*
• Long term macrolide and long term inhaled antibiotic	• Consider regular iv. antibiotics every 2-3months

P. Aeruginosa Colonized Patients

- Inhaled colistin for bronchiectasis pt with chronic PA infection (B)
- Inhaled gentamicin as a 2nd line alternative to colistin (B)
- Consider azithromycin or erythromycin as an alternative (e.g. intolerant to inhaled antibiotic) to an inhaled antibiotic (B)
- Consider azithromycin or erythromycin as an additive treatment to an inhaled antibiotic if having a high exacerbation frequency (D)

Non-P. Aeruginosa Colonized Patients

- Use azithromycin or erythromycin (A)
- Considered inhaled gentamicin as a 2nd line alternative to azithromycin or erythromycin (B)
- Consider doxycycline as an alternative in patients intolerance of macrolides or ineffective (C)

Long Term Antibiotic Treatment (≥3 months) in Step 3

- **MRC study in 1957**: n = 122, RCT to PCN 500mg qid or oxytetracycline 500mg qid for 2 days per week for 1 yrs [Anonymous 1957]
- **Clerniack in 1959**: n = 67, tetracycline (2g/d), penicillin G or placebo
- **Currie DC in 1990**: amoxicillin 3g bid for 32 wks

Long Term Antibiotic: Macrolide

- **Wong in *Lancet* 2012:**
  - AE ≥1, azithromycin 500mg TIW for 6 months
  - Exacerbation/pt = 0.59 vs. 1.57 ($p<0.001$, ↓62%), benefit greater in higher SGRQ
  - Benefit maintained in 6 months after cessation
- **Altenburg in *JAMA* 2013:**
  - AE ≥3, azithromycin 250mg qd vs. placebo for 1 year (n= 83)
  - Exacerbation/pt = 0.84 vs. 2.05 ($p<0.001$, ↓59%)
- **Serisier in *JAMA* 2013:**
  - AE≥2, erythromycin 250mg bid for 48 weeks (n = 117)
  - Exacerbation/pt = 1.29 vs. 1.97 ($p=0.003$, ↓35%)
  - Oropharygeal *streptococci* resistance = 27.7% vs. 0.04%

Long Term Antibiotic: Macrolide vs. Erythromycin

- **Guang Ying in *Pul Pharmaco Therapy* 2014:** (meta-analysis)
  - Lower exacerbation rate in azithromycin vs. erythromycin
  - The benefit of macrolide is more delayed in erythromycin than Azithromycin
- **BLESS trial in *Lancet RM* 2014:**
  - A reduced abundance of *H. influenza*, but increased abundance of *P. aeruginosa* in patients treated with erythromycin.
- **GP in BTS guideline**
  - Ensure no active NTM infection with at least one negative respiratory NTM culture
  - Starting dose azithromycin 250mg TIW, use carefully if patient has significant hearing loss
  - Review six monthly for efficacy, toxicity, sputum culture and sensitivity

Long Term Antibiotic: nebulized colistin

- A reduction of bacterial counts at the 28-day time point [Wilson 2013, Serisier DJ 2013]
- **Haworth 2014**: colistin 1MU bid (n= 73) vs. 0.45% saline (n = 71) bid for 6 months in chronic PA infection [AJRCCM 2014;189:975]
  - Time to next exacerbation = 165 vs. 111 days, p= 0.11
  - Time to next exacerbation in compliant population (≥80%) = 168 vs. 103 days, p=0.028
  - A significant reduction of PA count at 12 weeks
  - A significant reduction of SGRQ at 26 weeks
  - No difference in FEV1, sputum weight or adverse effects.

Long Term Antibiotic: nebulized ciprofloxacin

- **Serisier DJ 2013**: dual release ciprofloxacin for inhalation (DRCFI, AZ, liposomal 150mg in 3ml, free ciprofloxacin 60mg in 3ml) vs. placebo bid for 24 weeks in adult bronchiectasis with PA [n = 42, phase II, Thorax 2013;68:812]
  - DRCFI resulted in a mean 4.2 Log_{10} CFU/g reduction in PA bacterial density at day 28 compared with placebo
  - Median time to next exacerbation = 134 vs. 58 days (p = 0.057 ITT, 0.046 per protocol)

Long Term Antibiotic: dry powder inhalation of ciprofloxacin

- **RESPIRE 1:** patients with ≥2 exacerbation in previous year and positive sputum culture, 2:1 randomized to Cipro DPI 32.5mg bid or placebo 14 day on/off for 48 weeks [n= 416, phase III, ERJ 2018;51:1702052]
  - Prolonged median time to first exacerbation = 336 vs. 186 days, HR 0.53, p = 0.0005
  - Reduced mean number of exacerbation = 0.6 vs. 1.0

- **RESPIRE 2:** patients with ≥2 exacerbation in previous year and positive sputum culture, 2:1 randomized to Cipro DPI 32.5mg bid or placebo 14 or 28 day on/off for 48 weeks [n = 521, phase III, ERJ 2018;51:1702053]
  - Prolonged time to first exacerbation in 14 days on/off = HR 0.87, p 0.3965
  - Prolonged time to first exacerbation in 28 days on/off = HR 0.71, p 0.0511
  - Reduced rate of exacerbation in 14 days on/off = RR 0.83, p = 0.2862
  - Reduced rate of exacerbation in 28 days on/off = RR 0.55, p = 0.0014

Long Term Antibiotic: nebulized gentamicin

- **Murray MP 2011**: gentamicin 80mg bid vs. 0.9% saline for 12 months [n = 57, AJRCM 2011;183:491]
  - Reduced sputum bacterial density with 30.8% eradication in PA; 92.8% eradication in non-PA pathogens
  - Less purulent sputum = 8.7% vs. 38.5%, $p < 0.001$
  - Greater exercise capacity = 510 m vs. 415m, $p = 0.03$
  - Fewer exacerbation = 0 vs. 1.5, $p < 0.001$
  - Increased time to exacerbation = 120 d vs. 61.5 d, $p = 0.01$
  - Greater improvement of Leicester Cough Q and SGRQ
  - No difference in sputum volume, FEV1, FVC, or FEF25-75%

Safety in Long Term Antibiotic

- **Aminoglycoside**:
  - Avoid using if Ccr < 30ml/min
  - Use with caution if significant hearing loss or balance issues
  - Avoid concomitant nephrotoxic medications
- **Macrolides**
  - No active NTM infection with at least one negative respiratory NTM culture
  - Use with caution if significant hearing loss or balance issues
- **Colistin**
- **Ciprofloxacin/levofloxacin (po. Iv.)**

Long Term Antibiotic: intravenous antibiotic

- **Mandal P 2013**: n = 19, cyclic 8-wk iv antibiotics for 1 yr based culture sensitivity for 14 days, ≥5 exacerbation previous year, compared before with after tx
  - Reduction in the number of exacerbation = 9.3 vs. 8.0, p = 0.02
  - Reduction of Leicester cough Q ≥1.3 u in 63.2%
  - Reduction of SGRQ ≥4 in 42.1%
  - Increased exercise capacity by 58.7m

Bronchiectasis: case 1

Patient characteristics:

- Chen, 77 yr female, never smoker, occupation = NS, sinusitis (-), AR (-), GERD (-), PND(-)
- PH = DU + HP infection s/p eradication in 2011, glaucoma in 2015, NTM in 2018, hernia s/p surgery

Optimizing Tx: airway clearance, exacerbation, O2

- CM OPD (2019/5/15) = purulent sputum, s/p Augmentin, flumucil, xanthium
- CM OPD (2019/5/22) = flumucil, xanthium
  - C3, C4, IgG (H), IgA (H), IgM, IgG4 (H 215.2), RF (-), c/p-ANCA (-), SSA/SSB (-), ANA (80), anti-dsDNA (-)
  - Sialoscintigraphy: class III (severe dysfunction)
  - Total IgE = 136 , Eos count = 78/cumm, ESR = 70mm/hr, CRP = 6.67 mg/dl, ECP 17.4 ug/L
  - PFT (FVL and Lung volume), CXR

Assessment: pt understanding, dx progression, pathogens, underlying, comorbidities

Stepwise tx: step 1-2 (physiotherapy, mucoacitve agent)

- CM OPD (2019/6/19) = flumucil, xanthium, Duasma, prednisolone 5mg bid, eurodin

- **Hospitalization (2019/7/20-7/30)**

- hemoptysis 100-200ml and dyspnea
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- Lab (7/20): wbc 11600, Hb 11.6,PTL 356k, S/L 95/4%, Eos 0%, d-dimer =0.218 (<0.5 ug/l)
- Iv Antibitoic = Tazocin + Teicoplanin
- Combivent 1 vial UDV q6hv
- Duasma + prednisolone?

Reassesment

Stepwise tx: step 3 (long-term macrolide or inhaled antibiotic)

MBD: combivent 1vial bid +
Zithromax 250mg TIW + pred 5mg qd

Conclusions

- Complete assessment (pathogen, comorbidities..) and optimizing treatment (physiotherapy, macrolide, inhaled antibiotic..) in deteriorating patients with bronchiectasis
- Stepwise approach in managing patients with bronchiectasis
- Biomarker (EOS, FeNO..) for apply long-term ICS or OCS?