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Multidrug-resistant TB: management in a time of change

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Background

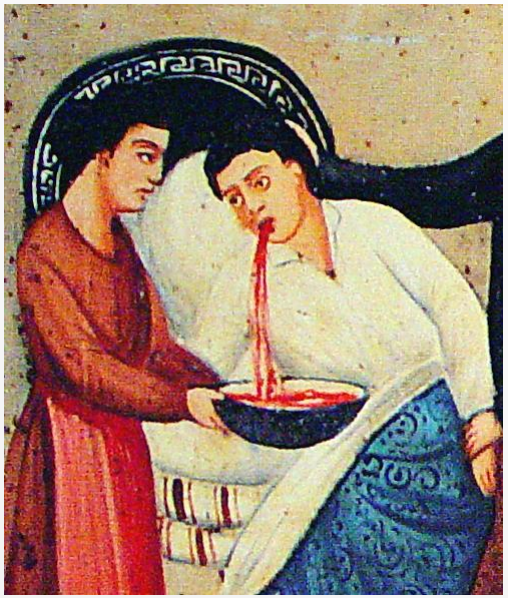
"Kate"

37 year old Caucasian, Manchester-born woman, previously fit and well

Works as sports teacher in 6th form college

Never smoked

Haemoptysis in July 2018



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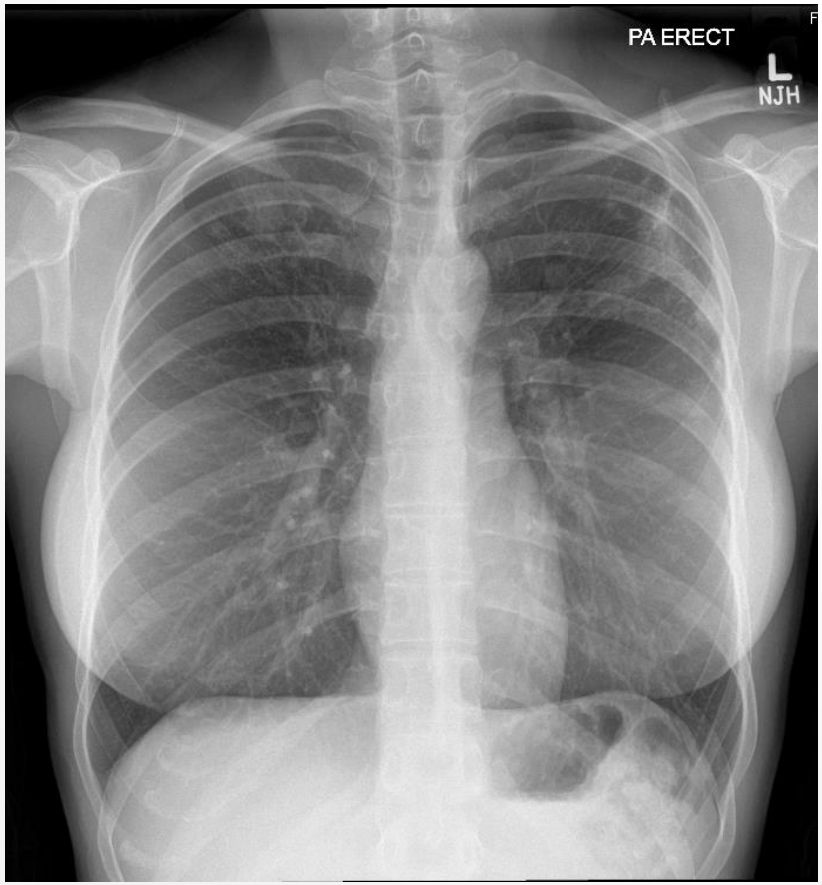
Chest consultations, August 2018

Family history of lung cancer
Long standing history of nasal congestion
No response to amoxicillin
CT scan viewed but not reported at that time

Travel:
- Mexico, 2016
- Cape Verde, 2016
- W. Europe



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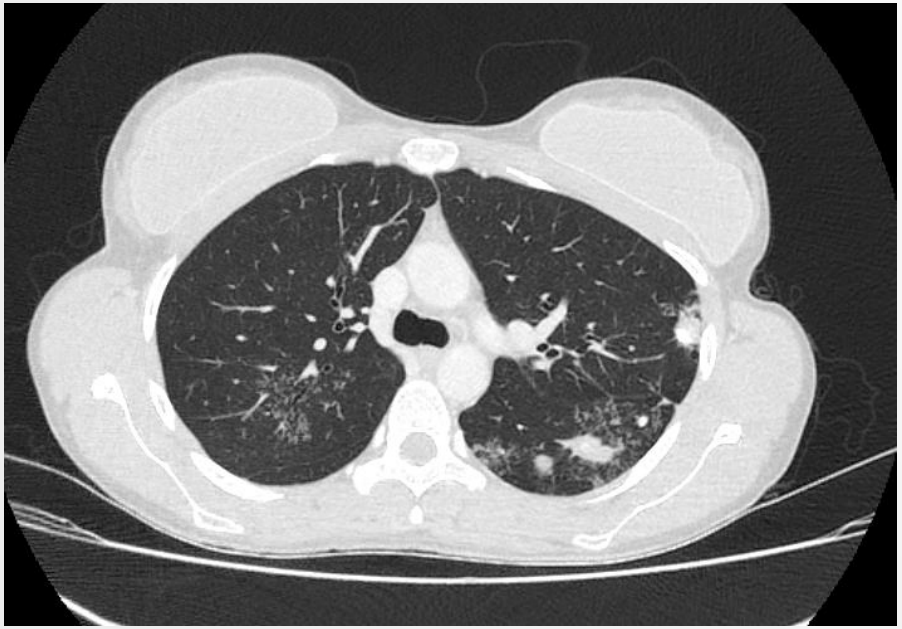
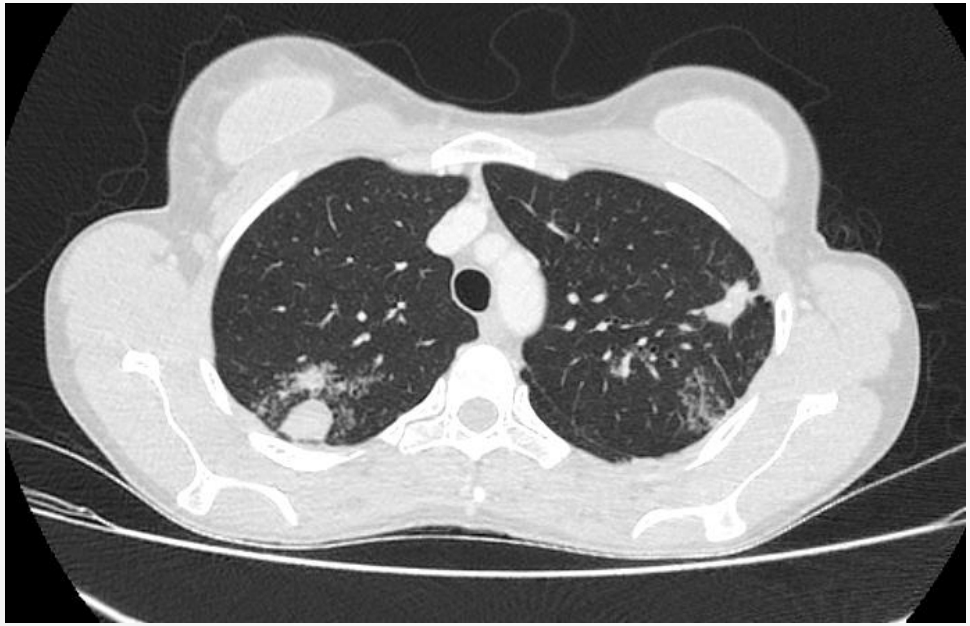
Chest consultations, August 2018





Chest consultations, August 2018

Many investigations initiated mid- August

- autoimmune screen
- Sputum for TB investigations x 6
- Aspergillus IgG (borderline positive at 43)
- Sputum MC&S – one sample grew *Aspergillus flavus*
- Histoplasma antibodies (in view of travel to Mexico)
- Sputum cytology

Except for the Aspergillus, everything is negative. It's early September and school opens again.

September 20th

One sputum sample from mid-August has grown a mycobacterium

- Identified as *M. tuberculosis*
- Initial molecular tests show rifampicin resistance (mutation in rpoB) and isoniazid resistance (mutation in katG)

- Kate is referred to TB nurses and infectious diseases
- Admitted directly to negative pressure room
- She is well, worried, concerned for colleagues and students
- She lives alone; no children; male partner; mother living nearby (close contact)

Treatment
What to do?

Treatment
What to do?

- Start standard TB therapy, since she has no risk factors for drug-resistance
- Start empirical MDR therapy, including fluoroquinolone and amikacin
- Start short (9-12 month) regimen, with 4 month intensive phase in hospital
- Consider home iv therapy for injectables
- Start all-oral regimen
- Wait for more information on drug susceptibility

What guidance is available?

NICE 2016

If the rapid diagnostic nucleic acid amplification test for rifampicin resistance is positive:

1. continue infection control measures until pulmonary or laryngeal disease has been excluded
2. **manage treatment along with a multidisciplinary team with experience of managing multidrug-resistant TB** (see section 1.8)
3. offer a treatment regimen involving at least 6 drugs to which the mycobacterium is likely to be sensitive
4. test for resistance to second-line drugs. **[new 2016]**

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NICE tuberculosis guidelines 2016

Regional multidrug-resistant TB network

TB control boards should consider setting up a regional multidisciplinary TB network to oversee management of multidrug-resistant TB. This could:

1. Identify and designate regional expert centres.
2. Ensure all healthcare professionals who suspect or treat a case of multidrug-resistant TB are informed about and have access to specialist advisory services for multidrug-resistant TB. This includes the designated expert centre in their regional network and may also include the national advisory service for multidrug-resistant TB (currently provided by the British Thoracic Society).
3. Ensure all cases of multidrug-resistant TB are discussed at the regional multidisciplinary TB team meeting in the local clinical network.
4. Formally consider and record the advice from the specialist advisory services for multidrug-resistant TB provided by the designated regional expert centre or the national advisory service for multidrug-resistant TB. **[new 2016]**

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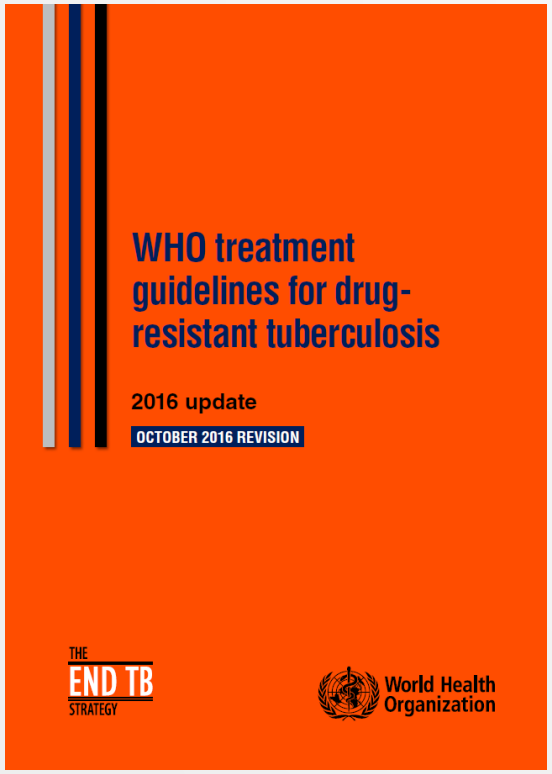
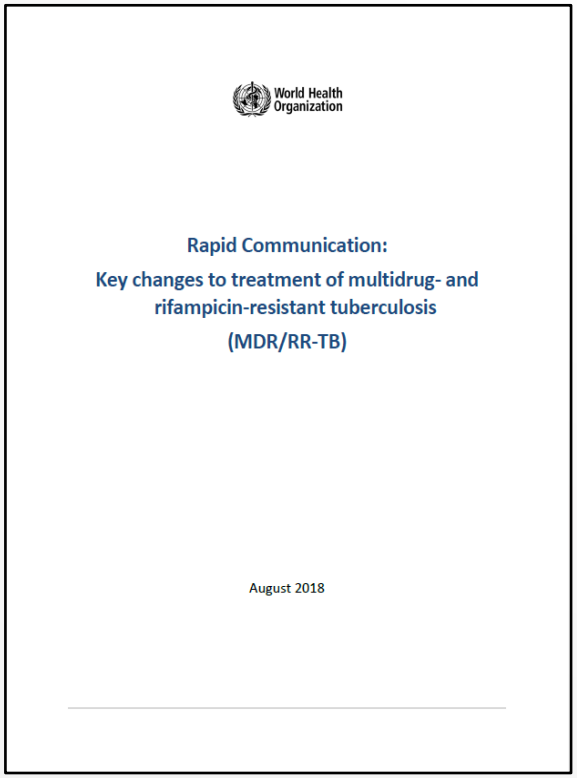
Further guidance outside of NICE





Fully revised new guideline document expected by end of 2018

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We waited for whole genome sequencing results, since they were likely to be available within 1-2 weeks and the patient was well. Kate was able to self-isolate at home; avoiding prolonged hospital admission.

Mycobacterium Whole Genome Sequencing Report from MGIT
Positive Samples

Report date: 05/10/2018 15:55:39
Report version: 1.7

Sample Details

Sequencing location:	Birmingham	Collection Date (dd/mm/yyyy):	13/08/2018 01:00:00
Local Lims Specimen ID:	180623788		
Plate name:	BG2796_MtubPilot	Sequencing date:	04/10/2018 10:58:03
Guuid:	35d1efd6-3275-4895-bebe-28084c44d587	Pipeline start date:	05/10/2018 13:30:42

Organism Identification

Kraken (percentage)

Human	0.00

Mykrobe		Percentage	Median
Phylo_group	Mycobacterium_tuberculosis_complex	99.69	40
Species:	Mycobacterium_tuberculosis	98.43	37
Lineage:	Beijing_East_Asia	100.00	38

Sequencing Quality Mapped to: R00000039

Total reads (~millions)	Mapped %	No reads mapped (~millions)	Coverage %
1.48	98.69	1.46	91.50

Resistance Summary

INH	RIF	EMB	PZA	QUI	SM	AG
R	R	S	S	S	R	S

Drug	Mutation	Nucleotides	Support (A/C/G/T)	Source	Prediction
INH	katG_S315T	AGC->ACC	(48/0/0/0) (0/47/0/0) (0/46/0/0)	Line-probe/derived-(471/480)	R
RIF	rpoB_S450L	TCG->TTG	(0/0/0/46) (0/0/0/44) (0/0/44/0)	Line-probe/derived-(290/294)	R
SM	rpsL_K43R	AAG->AGG	(59/0/0/0) (1/0/58/0) (0/0/61/0)	Line-probe/derived-(256/264)	R
Results from sensitive Line Probe					
MOX	gyrA_*94*	GAC->GAC	(0/0/44/0) (40/0/0/0) (0/43/0/0)	Line-probe	S
EMB	embB_*306*	ATG->ATG	(45/0/0/0) (0/0/0/42) (0/0/40/0)	Line-probe	S
INH	fabG1_*-15*	C->C	(0/41/0/0)	Line-probe	S

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Resistance Summary

INH	RIF	EMB	PZA	QUI	SM	AG
R	R	S	S	S	R	S

Interesting and helpful

Drug	Mutation	Nucleotides	Support (A/C/G/T)	Source	Prediction
INH	katG_S315T	AGC->ACC	(48/0/0/0) (0/47/0/0) (0/46/0/0)	Line-probe/derived-(471/480)	R
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EMB	embB_*306*	ATG->ATG	(45/0/0/0) (0/0/0/42) (0/0/40/0)	Line-probe	S
INH	fabG1_*-15*	C->C	(0/41/0/0)	Line-probe	S

bottom line

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2016

Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

2018

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

"Shorter" regimen:

4-6 months	**5 months**
Moxifloxacin	Moxifloxacin
Amikacin	Clofazimine
Prothionamide	Pyrazinamide
Clofazimine	Ethambutol
High dose isoniazid	
Pyrazinamide	
Ethambutol	

Treatment
What to do?

- Start standard TB therapy, since she has no risk factors for drug-resistance
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- Start short (9-12 month) regimen, with 4 month intensive phase in hospital
- Consider home iv therapy for injectables
- Start all-oral regimen
- Wait for more information on drug susceptibility (phenotypic?)

What does the patient want?

- minimal time in hospital
- minimal toxicity
- no injections
- shortest treatment possible
- to get life back to normal as soon as possible

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What does the patient want?

- minimal time in hospital
- minimal toxicity
- no injections
- shortest treatment possible
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GROUP	MEDICINE	Abbreviation	
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx	✓
	Bedaquiline[1,4]	Bdq	✓
	Linezolid[2]	Lzd	✓
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz	✓
	Cycloserine OR Terizidone	Cs Trd	
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E	✓
	Delamanid[3,4]	Dlm	
	Pyrazinamide[5]	Z	✓
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm	
	Amikacin (OR Streptomycin)[7]	Am (S)	
	Ethionamide OR Prothionamide	Eto Pto	
	p-aminosalicylic acid	PAS	

Local and national fora
- local MDR MDT
- BTS Clinical Advisory Service

How should we monitor treatment?

Is treatment working?

Drug toxicity?

How should we monitor treatment?

Is treatment working?

- sputum culture conversion
- radiological improvement
- inflammatory markers
- drug levels
- treatment adherence

Drug toxicity?

- Clinical symptoms and signs
- Biochemistry, haematology
- drug levels
- ECG for QT interval

Weeks 4 - 5

- Haemoglobin dropping; tingling fingers and toes

- QTc increases each week, from baseline 427ms, to 501ms

How should we approach contact tracing?

Recap:

- school teacher, sports, at 6th form college
- lives alone, has partner and close family members
- WGS indicates links to other cases nationally, but not locally

Current treatment

Started 28th September – now week 7

Bedaquiline
Levofloxacin
Cycloserine (+ pyridoxine)
Clofazimine
Pyrazinamide
Ethambutol

Short term plan

Induced sputum x 3; if culture converted release from isolation and repeat CT chest.
Need to see full 2018 guideline and may need more bedaquiline

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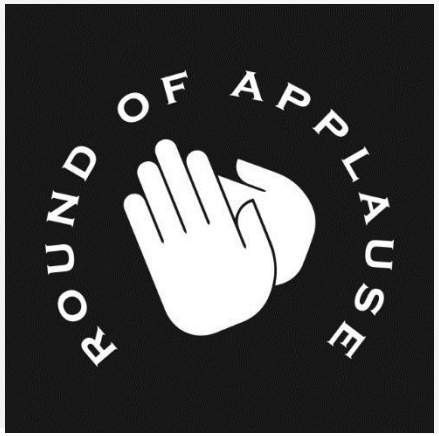
It's a lot of work for the specialist TB nurses, for which many thanks!



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Any questions?

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