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Primary capreomycin resistance is common, and associated with early mortality in extensively drug-resistant tuberculosis (XDR-TB) patients in KwaZulu-Natal, South Africa

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Abstract

Background—Capreomycin is a key antimycobacterial drug in treatment of extensively drug-resistant tuberculosis (XDR-TB). Drug susceptibility testing (DST) for capreomycin is not routinely performed in newly diagnosed XDR-TB in South Africa. We performed this study to assess the prevalence, clinical significance, and molecular epidemiology of capreomycin resistance in newly diagnosed XDR-TB patients in KwaZulu-Natal, South Africa.

Methods—Retrospective cohort study of consecutive XDR-TB patients admitted to a TB referral hospital without prior XDR-TB treatment. A subset of isolates had extended DST (including capreomycin), mutational analysis and IS6110 restriction fragment length polymorphism (RFLP) assays.

Results—216 eligible XDR-TB patients were identified. The majority were treated with capreomycin (72%), were young (median age 35.5) and female (56%). 165 (76%) were HIV+, and 109 (66%) were on antiretroviral therapy. A subset of 52 patients had full DST. 47/52 (90.4%) XDR-TB patients were capreomycin resistant. Capreomycin-resistant patients experienced worse mortality and culture conversion than capreomycin susceptible though this difference was not

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Conflicts of Interest

No conflicts of interest to declare.

statistically significant. The A1401G mutation in the *rrs* gene was associated with capreomycin resistance. The majority of capreomycin resistant strains were F15/LAM4/KZN lineage (80%), and clustering was common in these isolates (92.5%).

Conclusions—Capreomycin resistance is common in patients with XDR-TB in KwaZulu-Natal, is predominantly due to ongoing province-wide transmission of a highly resistant strain, and is associated with high mortality. Capreomycin should be included in routine DST in all XDR-TB patients. New drug regimens that do not include injectable agents should be operationally tested as empiric treatment in XDR-TB.

Keywords

extensively drug-resistant tuberculosis (XDR-TB); capreomycin resistance; South Africa; drug susceptibility testing

Introduction

Drug-resistant tuberculosis exacerbated by endemic HIV has been well described in KwaZulu-Natal, South Africa.¹⁻⁵ Extensively drug resistant tuberculosis (XDR-TB) is the most drug-resistant form of TB and is defined as *M. tuberculosis* (MTB) resistant to isoniazid, rifampicin, any fluoroquinolone drug and at least one of the three second-line injectable agents (kanamycin, amikacin, and capreomycin).⁶ A hospital-based outbreak of XDR-TB and HIV in Tugela Ferry, KwaZulu-Natal in 2005 attracted significant global attention to this syndemic.⁷

A key component of the current XDR-TB treatment regimen is capreomycin, an injectable antimycobacterial agent in the cyclic peptide class. Globally capreomycin is included in XDR-TB treatment regimens for its excellent bactericidal activity, and lack of availability of alternative bactericidal agents for densely drug-resistant MTB. Since 2006, in KwaZulu-Natal, South Africa, capreomycin has been available and is restricted for treatment of XDR-TB. Cross-resistance between aminoglycosides and capreomycin associated with polymorphisms within *rrs* gene has been described but the population-level prevalence of capreomycin resistance is unknown.^{8,9}

Drug-susceptibility testing (DST) is an essential aspect of the management of drug-resistant TB. However, full DST to second-line antimycobacterial agents is not routinely performed globally even in patients with known MDR-TB.¹⁰ Until recently, capreomycin DST was not routinely performed in KwaZulu-Natal outside of the research setting due to resource constraints. Current WHO guidelines on treatment of XDR-TB recommend that in the setting of resistance to aminoglycosides to use an injectable agent which the patient has not used before since clinical data on the efficacy of DST is limited.¹¹

We performed this study to determine the prevalence of capreomycin-resistance in XDR-TB patients prior to treatment with capreomycin-containing TB regimens in KwaZulu-Natal, South Africa, to elucidate the mechanism of capreomycin drug-resistance, and understand the clinical implications of capreomycin resistance for patients with XDR-TB.

Methods

Clinical

We performed a retrospective cohort study of all newly diagnosed, microbiologically confirmed, adult XDR-TB patients admitted from January 2008 to September 2010 in a public TB referral hospital in KZN. Eligible patients were adults with microbiologically confirmed XDR-TB by DST without prior therapy for XDR-TB. Demographics and clinical data were collected by retrospective chart review. TB culture results and routine first and second-line drug-susceptibility results were collected retrospectively through the clinical laboratory system. Treatment regimen was determined by the attending physician. The standard of treatment for XDR-TB was individualized therapy according to drug-susceptibility testing and patient tolerance. TB sputum culture conversion was defined as having >2 negative consecutive sputum cultures 30 days apart after initiation of treatment. Mortality was defined as all-cause mortality.

All eligible patients in the study were included in an analysis of risk factors for survival and culture conversion. Proportional hazards regression analysis was performed to assess factors associated with death and culture conversion. Cox proportional hazards were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) at 6 months after initiation of XDR-TB treatment. Significant variables or variables that caused >10% change in the univariate HR were included in the multivariate model. We calculated 95% CIs by using a normal approximation of the binomial distribution. The Fisher's exact test or χ^2 test was used to compare categorical variables. Kaplan-Meier survival curves for death and for time to culture conversion were calculated using standard techniques from time of XDR TB treatment initiation with appropriate anti-TB drugs. Time to culture conversion and mortality were censored at 6 months since long term follow up data are not available. Statistical analysis was performed using SAS version 9.2 software (SAS Institute, Cary, NC, USA).

Microbiology

Mycobacterium tuberculosis (MTB) isolates were sought for all patients from a time prior to initiation of XDR-TB treatment. If isolates prior to treatment were not available we included isolates from up to 3 months after initiation of treatment. These isolates were subcultured from stocks from the regional TB laboratory. Full DST including capreomycin testing was performed using the 1% proportional method on Middlebrook 7H11 agar using standard antibiotic concentrations (10ug/ml cut point).¹² Extended DST to determine moxifloxacin minimum inhibitory concentration (MIC) using clinically relevant cut points (0.125, 0.25, 0.5, 1, 2, 4, 8 ug/ml) was also performed.^{13,14} A commercial kit (Geno Type® MTBDRsl (Hain Lifescience, GmbH, Neheren, Germany) was used to probe for known resistance conferring mutations in the *rrs* gene.

Genotyping

Single MTB isolates of patients with capreomycin resistant XDR-TB were genotyped by performing IS6110 RFLP.^{15,16} Briefly, CTAB extracted genomic DNA was restricted with the restriction endonuclease PvuII, separated in a 1% agarose gel and immobilized onto a

Hybond-N+ nylon membrane (Amersham). IS6110-fragments were hybridized and detected using enhanced chemiluminescence (Amersham). Banding patterns were analyzed with BioNumerics version 6.6 (Applied Maths). Isolates were considered clustered if they had greater than 3 bands identical without discordant bands.

Ethics approval was obtained through the Boston University Medical Center Institutional Review Board and the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Results

We identified 216 adult patients during the study period with bacteriologically confirmed TB, DST consistent with XDR-TB, who had not undergone prior treatment for XDR-TB. (Table 1) Patients were predominantly female (56%), with a median age of 35.5 years, and TB treatment experienced (96% previously treated for TB).^{17,18} Eighty-four percent (165/197) of patients with a known HIV status were HIV co-infected. Forty-five percent of all patients (98/216) were AFB smear negative at treatment start. The majority of HIV co-infected XDR-TB patients (65%) were on antiretroviral therapy (ARV) and median CD4 T-cell count was 195 (IQR 105-302) at commencement of XDR-TB treatment. Patients were tested for resistance to 6 drugs (kanamycin, ofloxacin, isoniazid, rifampicin, streptomycin, and ethambutol) and on average were resistant to 5.7 drugs. Capreomycin susceptibility testing was not performed on these isolates as it was not clinically available during the study period. Patients were started on XDR-TB treatment regimens that included a median of 5 drugs (Figure 1). Capreomycin (72%) and para-aminosalicylic acid (PAS) (73%) were components of the XDR-TB treatment regimen for the majority of patients. Treatment strategy was determined by the resident physician, and 60/216 (28%) did not receive capreomycin. Among those who did not receive capreomycin as part of their regimen, 25/60 received an aminoglycoside, 25/60 received an alternative fluoroquinolone (moxifloxacin or ofloxacin).

During the first six months of treatment 49/216 (22.7%) patients died and 21.6% converted their sputum TB culture to negative. On multivariate analysis presence of moxifloxacin in the initial treatment regimen was associated with improved survival (HR 0.13 (95% CI: 0.031-0.54)) in the first 6 months of treatment (Table 2). Older age was significantly associated with increased mortality (HR 1.18 (1.02 – 1.37) per every 5 years of increased age). There were no factors independently associated with 6-month culture conversion (data not shown).

Fifty-two XDR-TB isolates (52/216, 24%) were identified and found to be viable for further testing. Minimum inhibitory concentration testing for capreomycin was performed using agar dilution method on 52 clinical isolates. Forty-seven (90%) XDR-TB patients were capreomycin resistant. 37/52 specimens were collected prior to initiation of XDR-TB treatment. Of the 37 samples collected prior to XDR treatment were 94% capreomycin resistant. Of the 15 samples collected after initiation of XDR-TB treatment, 80% were capreomycin resistant. This difference was not statistically significant ($p=0.13$). Samples collected after XDR treatment were collected mean 72 days after initiation (S.D. 45.5 days).

4/52 patients had been treated for MDR-TB with aminoglycosides previously. The Geno Type® MTBDRsl assay codons 1401, 1402 and 1484 of the *rrs* gene were analyzed. Mutations tested for included A1401G, C1402T and G1484T. Forty-seven (100%) of the capreomycin resistant isolates harboured the *rrs* A1401G mutation. None of the five capreomycin susceptible isolates had this mutation. Neither C1402T nor G1484T mutations were detected in any isolate. Despite the fact that all XDR-TB isolates were resistant to ofloxacin, 47% had MICs of less than 2 ug/ml for moxifloxacin (the proposed 'high' critical concentration for moxifloxacin drug-susceptibility) and 27% had MICs of 0.50 ug/ml or less (the proposed 'low' critical value).¹¹ (Supplemental Figure 1)

Patients with capreomycin resistant isolates (N=47) had lower rates of six-month TB culture conversion (25% vs. 60%) and higher mortality (20% vs. 0%) compared to patients with capreomycin susceptible isolates, but this difference was not statistically significant ($p=0.35$ and $p=0.0573$, respectively). (Figure 2a, 2b).

Of the 47 capreomycin resistant isolates, 44 (83%) were successfully genotyped using RFLP; no RFLP fingerprint patterns were obtained for 4 isolates despite DNA being present. Five different strain types were identified among the remaining 40 isolates (Supplemental Table 1). The F15/LAM4/KZN genotype which was identified in 35/40 (87.5%) patients, could be divided into 4 sub-clusters separated by copy number of a few *IS6110* elements. None of the patients was infected with a Beijing strain.

XDR-TB cases were mapped according to the home address of each patient. The initial reported XDR-TB outbreak was considered to be a point source outbreak in the Msinga subhealth district (Tugela Ferry). However, in our cohort patients reported home address in all 11 provincial health districts. In terms of RFLP genotyping, the F15/LAM4/KZN genotype was predominant, and wide-spread. (Figure 3a, 3b).

Conclusion

Our study highlights several important findings. A high percentage (90%) of newly diagnosed XDR-TB patients in KwaZulu-Natal were found to have primary capreomycin resistance (i.e. MTB isolates resistant to capreomycin, either prior to, or soon after first exposure to a capreomycin-containing regimen). Capreomycin-resistance was widespread with cases in all 11 provincial health districts. All capreomycin resistant isolates characterized in this cohort had the same A1401G mutation in *rrs* gene, a mutation known to confer capreomycin-resistance (and cross resistance to aminoglycosides), while no susceptible MTB isolates had this mutation. Capreomycin-resistant XDR-TB isolates were predominantly (80%) of the same MTB lineage (F15/LAM4/KZN genotype).¹⁹ While the majority of samples were in clusters (92.5%) by RFLP, there did not appear to be clustering at the patient's home locations, unlike the original Tugela Ferry outbreak.⁷ Although the majority were previously treated for TB (92%) few (8%) had documented previous treatment with aminoglycosides, making acquired capreomycin-resistance in the setting of cross-resistance with aminoglycosides unlikely. Taken together, these data suggest that capreomycin-resistance is predominantly due to primary transmission of a highly drug

resistant strain of MTB in KwaZulu-Natal.^{20,21} This hypothesis needs further confirmation in a population-based study of drug-resistant TB using whole genome sequencing.

Predictably, patients with capreomycin resistant XDR-TB experienced poor treatment outcomes with lower rates of TB culture conversion and higher mortality than patients with capreomycin-susceptible strains through 6 months. On multivariate analysis moxifloxacin was associated with improved early mortality. When we tested a subset of the MTB isolates for susceptibility to moxifloxacin 27% were moxifloxacin susceptible (based on WHO recommended critical concentration) despite being resistant to ofloxacin in standard testing.¹³ This suggests that the mortality benefit seen with moxifloxacin treatment in this cohort may be due to partial or complete susceptibility to moxifloxacin in a subset of XDR-TB patients in the context of near-universal capreomycin-resistance.

A recent study of XDR-TB patients in the Tugela Ferry area identified a high proportion of capreomycin resistance (89.5%), but only 19 isolates were tested and treatment outcomes were not reported.²² All patients were capreomycin resistant prior to treatment with either an amikacin or capreomycin suggesting primary transmission of a capreomycin resistant strain. Our study demonstrates that this phenomenon is considerably more widespread than previously believed. A European study identified capreomycin resistance as an independent risk factor for poor outcome in MDR-TB patients, but it was not clear how patients were treated, whether resistance was primary or secondary, or the molecular mechanism of resistance.²³

One study of XDR-TB treatment in South Africa identified moxifloxacin as significantly associated with survival in the first 12 months of treatment,²³ however this survival benefit was not seen with prolonged follow up.²⁴ Moxifloxacin has been recommended by experts for treatment of XDR-TB despite fluoroquinolone resistance,²⁵ and a meta-analysis of XDR-TB treatment supported the inclusion of later generation fluoroquinolones in XDR-TB treatment.²⁶ Laboratory studies have been inconclusive regarding the degree of cross-resistance between early and later generation fluoroquinolones, although mouse studies support the use of moxifloxacin in the treatment of XDR-TB. The clinical benefit of later generation fluoroquinolones in isolates which are resistant to earlier generation quinolones is poorly characterized.²⁷

Our study has several limitations to generalizability including having only a subset of isolates for extended DST and molecular testing. We attempted to retrieve all available MTB isolates from an operational, provincial TB laboratory but only 24% were located and culturable. Another limitation is that the small number of patients with capreomycin-resistance (N=5) means that we have insufficient power to show a difference between the groups. Since complete genomic sequencing was not performed it is possible that the *rrs* mutation reported was not the only contributor to capreomycin resistance. It is possible that with whole genome sequencing we could further discriminate the genotypic clustering seen on RFLP, or that with a larger sample other patterns of RFLP clustering would emerge. Finally since we did not have access to long term follow up data, the 6-month outcome results obtained may not reflect treatment outcomes at 24 months, or end of treatment relapse free-survival.

In conclusion primary capreomycin-resistant XDR-TB in KwaZulu-Natal, South Africa is common, geographically widespread, associated with RFLP clustering, is predominantly of a single MTB lineage, and appears to be associated with poor 6-month culture conversion and survival. Full first and second-line DST, including capreomycin susceptibility, should be included in routine DST of all patients with XDR-TB. New drug regimens, which do not depend on capreomycin should be operationally tested urgently as empiric treatment in XDR-TB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Initial XDR-TB treatment regimen for XDR-TB patients on treatment (N=216)

Figure 2.

a. Kaplan- Meier mortality among XDR-TB patients with full DST (N=52) stratified by Capreomycin resistance

b. Kaplan- Meier time to culture conversion among XDR-TB patients with full DST (N=52) stratified by Capreomycin resistance.

Figure 3.
Geographic distribution of the origin of XDR-TB cases in KwaZulu-Natal, South Africa.
A. Distribution of all XDR-TB cases by home address (N=210)
B. Distribution of capreomycin-resistant XDR-TB cases by home address (N=47)

Table 1

Demographic Characteristics of Eligible XDR-TB Patients Admitted to King DinuZulu Hospital during the Study Period (N=216), and the subset with extended DST and genotyping (N=52)

	All XDR-TB patients N=216 (%)	XDR-TB Patients with isolates for DST and genotyping N=52 (%)	XDR-TB patients <i>without</i> isolates for DST and genotyping N=164 (%)	p-value Patients with DST vs. no DST
Sex				
Male	95 (44)	26 (50)	69 (42)	0.32
Female	121 (56)	26 (50)	95 (58)	
Age				
≤35 years	108 (50)	24 (46)	84 (51)	0.52
>35 years	108 (50)	28 (54)	80 (49)	
Median age, years:	35.5	36.5		
Body Mass Index				
Obtained	99 (46)	25 (48)	74 (45)	0.71
Not Obtained	117 (54)	27 (52)	90 (55)	
Median (IQR)	19 (16-23)	18 (16-23)		
HIV Status				
Infected	165 (77)	44 (84)	121 (74)	0.19
Uninfected	32 (14)	5 (10)	27 (16)	
Unknown	19 (8)	3 (6)	16 (10)	
CD4 T-cell* Count (cells/mm ³)				
Known	93 (56)	25 (57)	68 (56)	0.40
Not Determined	72 (44)	19 (43)	53 (44)	
Median (IQR)	195 (105-302)	192 (112-234)		
ARV*				
Yes	114 (69)	31 (70)	83 (69)	0.82
No	51(31)	13 (30)	38 (31)	
Previous TB Treatment				
Yes	207 (96)	51 (98)	156 (95)	0.37
No	9 (4)	1 (2)	8 (5)	
Initial AFB Smear				
Positive	108 (50)	30 (58)	78 (47)	0.38
Negative	98 (45)	22 (42)	76 (46)	
Unknown	10 (5)	0	10 (6)	
Health Care Worker				
Yes	16 (7)	3 (6)	13 (8)	0.61

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	All XDR-TB patients N=216 (%)	XDR-TB Patients with isolates for DST and genotyping N=52 (%)	XDR-TB patients <i>without</i> isolates for DST and genotyping N=164 (%)	p-value Patients with DST vs. no DST
No	200 (93)	49 (94)	151 (92)	

* Among HIV infected.

Table 2
Risk factors for Mortality among XDR-TB Patients on Treatment Six Months after Initiation of Treatment

Variable	Mortality (n/N)	Univariate analysis		Multivariate analysis	
		Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Capreomycin					
No	18.3% (11/60)	1.00 (ref)	-	1.00 (ref)	-
Yes	24.4% (38/156)	1.39 (0.71 – 2.72)	0.3387	1.68 (0.83 – 3.41)	0.1486
Moxifloxacin					
Yes	4.1% (2/49)	0.127 (0.032-0.54)	0.0049	0.13 (0.031-0.54)	0.0051
No	28.1% (47/167)	1.00 (ref)	-	1.00 (ref)	-
Gender					
Male	16.8% (16/95)	1.00 (ref)	-	1.00 (ref)	-
Female	27.3% (33/121)	1.70 (0.94 – 3.09)	0.0806	1.83 (0.96 – 3.49)	0.0675
Age (by 5 year increase)		1.12 (0.97 – 1.29)	0.1153	1.18 (1.02 – 1.37)	0.0310
Previously treated for TB					
Yes	22.2% (46/207)	1.00 (ref)	-	1.00 (ref)	-
No	28.6% (2/7)	1.25 (0.30 – 5.14)	0.7589	0.97 (0.23 – 4.03)	0.9629
HIV status					
Negative	15.6% (5/32)	1.00 (ref)	-	1.00 (ref)	-
Positive	23.6% (39/165)	1.55 (0.61 – 3.94)	0.3535	1.85 (0.65 – 5.26)	0.2471
Unknown	26.3% (5/19)	1.73 (0.50 – 5.97)	0.3877	3.63 (0.94 – 14.09)	0.0623
ARV (HIV+ only)					
Yes	22.0% (24/109)	1.00 (ref)	-		
No	26.8% (15/56)	1.23 (0.65 – 2.35)	0.5264		