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Research Article

Ticarcillin Hypersusceptibility in Pseudomonas Aeruginosa in Cystic Fibrosis

Abstract

Background: A subpopulation of *Pseudomonas aeruginosa* (PsA) exists in cystic fibrosis (CF) patients that is hypersusceptible to ticarcillin, a carboxypenicillin, *in vitro* (Tic^{hs} strain) defined as a minimum inhibitory concentration (MIC) ≤4μg/ml.

Methods: In a retrospective cohort study, isolates of PsA from CF (23), non-cystic fibrosis bronchiectasis (NCFB) (17) and control (18) patients were analysed. MICs for each isolate were determined using agar dilution against six antibiotics and interpreted using EUCAST breakpoints. Prevalence of Tic^{hs} in each cohort was calculated. A point prevalence survey was conducted in CF to review the patients' clinical progress following PsA isolation.

Results: Prevalence of the Tic^{hs} strain in PsA was 48%, 76% and 0% in the CF, NCFB and control cohorts respectively. A statistically significant difference in geometric mean MIC was seen between the Tic^{hs} and non-Tic^{hs} cohorts in CF for ticarcillin (as expected) and temocillin (p=0.041and p=0.036 respectively). A similar trend was observed in NCFB for ticarcillin (p=0.038) and temocillin (p=0.067), although statistical significance was not reached for the latter.

In CF, the Tic^{hs} strain demonstrated lower MICs to all antibiotics tested apart from gentamicin compared to their non-Tic^{hs} counterparts. Those who had the Tic^{hs} strain in CF had fewer antibiotics (13.9 days versus 23.5 days, Tic^{hs} and non-Tic^{hs} respectively) although this result was not statistically significant p=0.202.

Conclusion: Our data supports the existence of a Tic^{hs} strain of PsA in our CF and NCFB patient populations. This strain correlated with reduced MICs to temocillin in CF, to which PsA would normally be resistant, which may be of clinical relevance.

Introduction

Pseudomonas aeruginosa (PsA) is the commonest organism cultured from sputum of adult CF patients, with approximately 80% of patients being infected by the age of 18 [1,2]. Antibiotic resistance in PsA is a growing problem with prevalence of multi-drug resistant *pseudomonas aeruginosa* (MDRPA) in CF reported as high as 35% amongst some adult CF centres [3]. One study found CF related diabetes, long-term inhaled tobramycin use and frequent acute pulmonary exacerbations requiring hospitalisation or intravenous antibiotics to be independent risk factors for MDRPA [4].

Ticarcillin-clavulanate, a caboxypenicillin is sometimes used in combination to treat PsA pulmonary exacerbations in CF. The existence of an intriguing subpopulation of PsA that is hypersusceptible to carbenicillin *in vitro* (defined as a minimum inhibitory concentration [MIC] ≤4μg/ml) in the sputum was first described in the 1970s [5,6]. Interestingly, majority of these strains were isolated from CF patients who are often colonised and/or infected with multi-resistant strains of PsA. Early studies reported a prevalence of this hypersusceptible strain in the CF sputums to be as high as 27%-55% and found these strains to be distributed evenly among the mucoid and non-mucoid populations of PsA [5,6]. Several studies have since found that this hypersusceptible strain, dubbed Tic^{hs} contains mutations in MexAB-OprM (which exports β-lactams, fluoroquinolones, tetracyclines, macrolides, chloramphenicol and trimethoprim) and MexXY (exports aminoglycosides, tetracycline and erythromycin) efflux pumps [7-9].

Temocillin is a semi-synthetic 6-α-methoxy derivative of ticarcillin and is used to treat exacerbations in CF patients, especially those colonised with *Burkholderia cepacia* [10,11].

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However, PsA is intrinsically resistant to temocillin with reported high MICs (128-256mg/L) [10-13]. This is thought to relate to poor permeation across the outer membrane, efflux pumps and/or reduced binding to penicillin binding proteins [10]. Buyck et al., demonstrated the Tic^{hs} strain in CF to also be hypersusceptible to temocillin, with MICs ranging between 1 and 4 [8]. The authors concluded that temocillin could contribute to the eradication of PsA in this Tic^{hs} population. A more recent publication found 29% of their 333 CF PsA isolates to have temocillin MICs ≤16 mg/L and 30-60% of these were resistant to conventional antipseudomonal antibiotics, making temocillin a very attractive therapeutic option [9].

Our aim was to determine the prevalence of the Tic^{hs} strain in chronic PsA isolates from our cohort of CF patients and to compare this to NCFB patients and controls. We also examined the impact of the Tic^{hs} strain on temocillin and other anti-pseudomonal antibiotics. Finally, we attempted to assess the clinical implications of Tic^{hs} on CF patients.

Methods

Study design, sample collection and laboratory processing

A retrospective observational cohort study at the All Wales Adult Cystic Fibrosis Centre (AWACFC), University Hospital of Llandough, United Kingdom was performed between 2013 and 2015. Isolates of PsA from clinical specimens are stored in frozen conditions at -80C at our laboratory. 23 isolates of PsA from sputum of CF patients and 17 PsA isolates from sputum of NCFB were retrieved from the freezer and compared to 18 isolates of PsA recovered from blood cultures, tissues, bone and joint fluid from control patients without pre-existing lung disease. Control PsA samples were obtained from sites other than sputum because isolation of PsA from sputum usually indicates underlying chronic lung disease and therefore it is impossible to collect sputum growing PsA from patients who have structurally normal lungs. Laboratory processing of samples was conducted in accordance with the local standard operating procedures which are derived from the UK Standards for Microbiology Investigations guidance [14].

Agar dilution was performed on Mueller Hinton agar using log2 dilutions of all antimicrobials in the range 0.008mg/L to 128mg/L using a standardised method [15]. MICs were interpreted using EUCAST breakpoints (version 7.1) [12]. *E.coli* NCTC 10418, *E.coli* ATCC 25922 and *P.aeruginosa* ATCC 27853 were used as control strains in all the experiments conducted.

Sputum from CF patients and NCFB patients were collected from adult patients attending dedicated outpatient clinics at the University Hospital of Llandough. Respiratory samples were processed according to the laboratory standardised operating procedure and samples growing PsA are usually stored in the freezer. These PsA isolates and the PsA isolates from controls were tracked through an electronic database and were retrieved from the freezer. For each cohort the prevalence of the Tic^{hs} strain of PsA was calculated and the geometric mean MICs were compared between the different groups.

For the CF cohort, we attempted to assess the clinical implications of the Tic^{hs} strain. We conducted a point prevalence survey to review antimicrobial prescription and clinical parameters at the time of PsA isolation. We followed up the CF cohort over a one year period to assess the number of antibiotic days, number of hospital admissions and FEV_1 at annual review and best FEV_1.

Statistical analysis

Statistical analysis was performed using R (version 3.2.2) using descriptive, ANOVA, Mann Whitney U Test, and regression analyses.

The CF and NCFB cohorts had two sub groups (Tic^{hs} and Non-Tic^{hs} strains) and sample sizes were unequal. A one way ANOVA (confidence intervals at 2.5% and 97.5%) test and the dependent 2-group Wilcoxon rank sum test with continuity correction were used. Multiple regression was used to investigate whether there was a significant difference between antibiotics upon comparison of the three groups.

In the CF cohort the subgroups Tic^{hs} and non-Tic^{hs} PsA cohorts were directly compared. We used a Welch Two Sample t-test with a 95% confidence interval. P-values of <0.05 were considered significant.

Results

Demographic characteristics

Cystic Fibrosis patients: Twenty-three CF patients with chronic PsA colonisation were assessed in this study (Table 1). The mean age was 31.3 years ± 8.8 years (age range-19 to 54). 70% of this cohort was female. The patients in the CF cohort had more female patients compared to the NCFB and control cohorts. CF patients were younger than patients in the two other cohorts as would be expected. The average duration of colonisation with PsA was 14 years. Patients were frequently colonised with multiple organisms. During the study period two patients had lung transplants and two patients died of CF related complications.

Non-Cystic Fibrosis Bronchiectasis patients: Seventeen PsA samples from twelve NCFB patients were assessed. For two patients several different strains of PsA were included in the analysis. The mean age was 63.6±10.9 years (age range- 41 to 76). 42% of this cohort was female. The average duration of colonisation with PsA in our NCFB cohort was 6 years. Within the NCFB cohort, only two patients were treated with antibiotics for an infective exacerbation at the time PsA was isolated in their sputum for this study. The mean duration of antibiotics was 14 days. The mean FEV_1 in this cohort was 1.24L and the mean percentage predicted FEV_1 was 57%.

Control patients

In our control group of 18 patients, the mean age was 68.6±21.9 years (age range- 5 to 91). 50% of the cohort was female.

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Prevalence of the Tichs strain and antibiotic susceptibilities

The prevalence of the Tic^{hs} strain in PsA in our cohort of CF patients was 48% compared to a prevalence of 76% in the NCFB cohort and 0% in controls. Resistant strains of PsA were more prevalent in the CF patients compared to NCFB patients and controls, except for temocillin and ticarcillin (Table 2). Interestingly, the MIC50 for ticarcillin in the CF cohort was 4 fold lower than the MIC50 for ticarcillin in the controls. For temocillin, the MIC50 was 16 fold lower in the CF cohort compared to the controls.

We calculated the geometric mean MICs for each antibiotic for each cohort (CF and NCFB, Tic^{hs} and non-Tic^{hs}) (Table 3). In the CF cohort, the Tic^{hs} strain was associated with reduced MICs to most antibiotics compared to their non-Tic^{hs} counterparts (apart from gentamicin) in a phenomenon described previously [4]. A statistically significant difference in geometric mean MIC between the Tic^{hs} and non-Tic^{hs} cohorts in CF was seen for ticarcillin, as to be expected, and temocillin (p=0.041and p=0.036 respectively).

In the NCFB cohort a similar trend of reduced MICs with the Tic^{hs} strain was observed compared to the non-Tic^{hs} strain for all antibiotics apart from ciprofloxacin, with a statistically significant difference in geometric mean MIC seen again for ticarcillin (p=0.039). A marked reduction in geometric mean MIC was seen between the two groups for temocillin (geometric mean MIC 1.79 in Tic^{hs} versus 64 in non-Tic^{hs}) but these findings were just under the threshold of reaching statistical significance (p=0.06).

Table 1: Baseline characteristics of the study population.

Characteristic	CF N=23	NCFB N= 17	Controls N= 18
Age (mean ± SD), years	31.3± 8.8	63.6±10.9	68.6±21.9
Sex, n (%)			
• Female	16 (70)	5 (42)	9 (50)
• Male	7 (30)	7 (58)	9 (50)
FEV_1, litres			Not applicable
• Mean FEV_1	2.09	1.24	
• % Predicted FEV_1	62%	57%	
BMI (mean ± SD) kg/m^2	21.9 ±3.4	28±3.8	Not available
Additional organisms cultured, n (%)			
• *Staphylococcus aureus*	21 (91%)	2 (12%)	Not applicable
• *Burkholderia cepacia*	1 (4%)	-	
• *Serratia marcescens*	4 (17%)	-	
• *Stenotrophomonas maltophilia*	7 (30%)	1 (6%)	
• *Acinetobacter baumanii*	2 (9%)	-	
• *Enterobacter sp.*	2 (9%)	1 (6%)	
• *Escherichia coli*	1 (4%)	1 (6%)	
• *Proteus mirabilis*	-	1 (6%)	
• *Klebsiella pneumoniae*	-	2 (12%)	
• *Morganella morganii*	-	1 (6%)	
• *Achromobacter xylosoxidans*	1 (4%)	-	
• *Aspergillus sp.*	9 (39%)	2 (12%)	
• *Penicillium sp.*	3 (4%)	1 (6%)	
• *Exophiala sp.*	1 (4%)	1 (6%)	
• *Mycobacterium sp.*	5 (22%)	1 (6%)	

Cystic fibrosis- clinical outcomes

We conducted a point prevalence survey for patients within the CF cohort, to evaluate the clinical outcomes at the time PsA was isolated in the sputum. Of the 23 CF patients, all were colonised chronically with PsA, 14 (61%) were treated with antibiotics for an infective exacerbation of their CF. Patients received a combination of two or three antibiotics to treat the CF exacerbation. The mean duration of antibiotics to treat this episode was 15.1±5.4 days (range 8 to 24 days).Of those admitted the mean length of stay in hospital was 13 days; the mean FEV_1 on admission was 1.3L and on discharge was 1.7L.

We reviewed the clinical progress and outcomes of the CF patients during the 1 year period following PsA isolation for this particular episode (Table 4). We excluded patients who died or had a transplant from this analysis. A mean of 18 days of total (hospital and home) IV antibiotics were required over a one year period. A key finding in this study was that those who had the Tic^{hs} strain of PsA in CF had fewer antibiotics (total antibiotics-13.9 days versus 23.5 days, Tic^{hs} and non-Tic^{hs} respectively) although this result was not statistically significant p=0.2883.

Discussion

This study demonstrates that a significant proportion of our adult patients with CF tested over a 2 year period are colonised and/ or infected with the ticarcillin hypersusceptible strain of PsA. 48% of our CF patients tested carried this strain.

Table 2: MIC range, MIC 50, MIC 90 and % resistant and % sensitive PsA isolates for CF patients, NCFB patients and controls (C).

	Meropenem			Ceftazidime			Ticarcillin			Temocillin			Ciprofloxacin			Gentamicin		
	CF	NCFB	C	CF	NCFB	C	CF	NCFB	C	CF	NCFB	C	CF	NCFB	C	CF	NCFB	C
MIC range	0.008-16	0.008-32	0.008-8	0.125-128	0.125-64	2-16	0.125-128	0.125-16	1-128	0.5-128	0.064-128	8-128	0.03-16	0.032-32	0.03-4	1-64	0.032-4	0.25-4
MIC 50	0.5	0.125	0.125	4	1.5	4	8	1	32	8	4	128	1	0.25	0.06	2	0.25	1
MIC 90	4	4	1	128	8	16	128	128	128	128	128	128	4	32	0.5	64	2	2
%R	21%	6%	6%	28%	12%	16%	36%	18%	74%	NA	NA	NA	63%	47%	7%	32%	0%	0%
%S	79%	82%	94%	72%	88%	84%	64%	82%	26%	NA	NA	NA	37%	53%	93%	68%	100%	100%
EUCAST BP	S≤2, >8 R			S≤8> R			S≤16> R			NA			S≤0.5 ≥ R			S≤4> R		

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Table 3: Geometric mean MICs of Tic^{hs} strain and non-tic^{hs} strain: CF versus NCFB.

	CF			NCFB		
	Geometric mean MIC (Tic^{hs} strain) n=11	Geometric mean MIC (Non-Tic^{hs} strain) n=12	P value	Geometric mean MIC (Tic^{hs} strain) n=13	Geometric mean MIC (Non-Tic^{hs} strain) n=4	P value
Meropenem	0.67	2.93	0.989	0.12	1.19	0.4075
Ceftazidime	5.04	28.45	0.143	1.24	19.03	0.6216
Ticarcillin	1.39	62.0	0.041	0.69	76.11	0.0387
Temocillin	4.15	61.67	0.036	1.79	64.00	0.0677
Ciprofloxacin	1.34	3.33	0.593	0.92	0.30	0.1363
Gentamicin	13.6	5.70	0.444	0.28	0.50	

Table 4: Tic^{hs} PsA versus Non-Tic^{hs} PsA in Cystic Fibrosis.

Mean values	Tic^{hs} PsA CF n=9	Non-Tic^{hs} PsA CF n=11	P value and confidence interval
Total number of IV antibiotic days over 1 year	13.9	23.5	0.2883 (95% CI -35.5 to 7.4)
Hospital IV days	9.67	12	0.5781 (95% CI -19.0 to 23.5)
Home IV days	12.2	35	0.2359 (95% CI -138.9 to 28.9)
Number of admissions/ year	1.8	1.9	0.7893 (95% CI -8.9 to 3.9)
FEV_1 at annual review	2.29	2.09	0.5469 (95% CI -1.1 to 2.0)
Best FEV_1	2.49	2.36	0.9453 (95% CI -0.9 to 2.1)

Rates of the Tic^{hs} strain in CF PsA previously reported have been variable (28% [5,9] to 55%[6]). This Tic^{hs} strain was also found in high prevalence in our NCFB cohort (76%). We are the second study to look at the prevalence of Tic^{hs} in this cohort since the original study where a prevalence of 62% was reported in NCFB[5].

The Tic^{hs} strain is of great interest to both microbiologists and CF physicians due to the *in vitro* hypersusceptibility it can demonstrate to several antimicrobials which can be of significant clinical benefit. A recent study by Chalhoub et al. called for the introduction of routine susceptibility testing of temocillin for PsA from CF patients [9]. Several studies have attributed the Tic^{hs} phenotype to the inactivation of the MexAB-OprM efflux pump in PsA, which usually confers significant resistance to antibiotics when overproduced [6-9]. However, it is not possible to definitively comment on precise mechanisms of resistance in our isolates as we did not determine these in our study.

A discernible finding in our study was the statistically significant difference in geometric mean MICs seen for ticarcillin and temocillin in the CF Tic^{hs} cohort compared to the CF non- Tic^{hs} cohort (p=0.041 and p=0.036 respectively). These findings were seen again in the NCFB Tic^{hs} cohort, although statistical significance was not met for temocillin (p=0.067). Traditionally temocillin has no activity against PsA due to its poor permeation across PsA outer membrane, efflux pumps and/or reduced binding to penicillin binding proteins [10]. However, this finding of a drop in temocillin MICs in Tic^{hs} has led to the hypothesis that temocillin may be used in the eradication of PsA in this particular cohort [8,9]. The Tic^{hs} strains of PsA were also hypersusceptible to other β lactam antibiotics compared to their non-Tic^{hs} counterparts (table 3). Although these results were not statistically significant there maybe clinical utility to this finding.

The clinical implications of the Tic^{hs} phenotype have never been studied. We conducted a point prevalence survey in an attempt to assess the impact of Tic^{hs} in CF. A notable observation in this study was that CF patients with the Tic^{hs} strain required fewer days of total antibiotics over a one year period than those without this strain. However these findings did not meet statistical significance and further work would be required with to assess this further.

Despite the laboratory observations, it is important to note that *in vitro* susceptibilities of Tic^{hs} strains often do not represent the 'real life' susceptibility of the organism, particularly within the CF lung where organisms live within complex biofilms. In addition, the existence of multiple strains of PsA in the chronic CF lung is well recognised and assessing the inter-bacterial relationships as to whether or not there is a dominant organism is extremely challenging. The differences in PsA lung biofilms and biofilms within other sites such as prosthetic joints has not been studied. It would be of interest to investigate whether the latter patient group, particularly patients with recurrent prosthetic joint infections with PsA, possess the Tic^{hs} strain and the clinical implications of this. It is postulated that the Tic^{hs} strain may provide a survival advantage to PsA, particularly within the hostile environments within CF airways. This may explain the higher prevalence of the Tic^{hs} strain in the CF and NCFB cohorts compared to controls where the Tic^{hs} strain was absent. Another hypothesis for the prevalence of this strain could be the use of broad spectrum, intravenous antibiotics in the CF/NCFB cohorts, thus selecting out the Tic^{hs} strain in this population compared to controls.

The main limitation of this study is the small sample size in each group which may affect the precision of our results. The PsA isolates used were obtained from frozen conditions which may impact on the phenotypic characteristics and resistance patterns observed. Five isolates from the CF cohort and one isolate from the NCFB cohort did not grow on the medium of choice and required MIC determination by gradient strip which may affect the validity of our results. We did not study the underlying mechanisms of resistance contributing to the Tic^{hs} phenotype which would be interesting to observe.

Further studies are needed with larger sample sizes and longer follow up periods to observe clinical outcomes, particularly those patients with the Tic^{hs} strain who received

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temocillin. Another interesting avenue to explore would be to investigate whether the Tic^{hs} strain exists in other settings of chronic pseudomonal infections such as bone and joint infections and examine the clinical implications of this.

Conclusion

In conclusion, our data supports the existence of the Tic^{hs} strain of PsA in CF and NCFB patients and had the highest prevalence in our NCFB cohort. In CF, this strain demonstrated statistically significant reduction in MICs *in vitro* to temocillin, to which PsA is conventionally resistant to. This is an important finding in an era of increasing multi-drug resistance and the scarcity in production of new antimicrobials, where temocillin, often used to treat *Burkholderia cepacia* in CF may provide an attractive option in also treating PsA. Our study adds to the evidence to support routine susceptibility testing of temocillin for all PsA isolates from CF and NCFB patients. Further studies are required to follow up the longer term outcomes of patients with the Tic^{hs} strain.

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Author contributions

IH conducted the laboratory research for the CF and control cohorts, analyzed the data and drafted the manuscript. TO conducted laboratory research for the NCFB cohort. AS performed the statistical analysis. MW assisted substantially with laboratory research and critically revised the manuscript. JD collected clinical data, provided patient sputum samples and reviewed the manuscript. RD conceived the study and critically revised the manuscript. All authors have approved the final manuscript.

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