4CPS-053 OUTCOMES OF INFRADOSED ANTIMICROBIALS PATIENTS WITH BACTEREMIA IN THE EMERGENCY DEPARTMENT

[1]A Monje*, [1]S Ojeda, [2]B Torrecilla, [1]J Ruiz, [1]A Plaza, [1]A Juanes. *[1]Hospital de la Santa Creu I Sant Pau, Pharmacy, Barcelona, Spain; [2]Hospital de la Sant Creu Y Sant Pau, Pharmacy, Barcelona, Spain*

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Background and Importance Bacteremia is a major cause of sepsis and is associated with high morbidity and mortality. Suboptimal antibiotic dosing in the bacteraemic population has previously been associated with poorer outcomes in the Emergency departments (ED).

Aim and Objectives This study has been designed to analyse clinical outcomes in patients with bacteraemia when receiving suboptimal antibiotic dosing (SAD).

Material and Methods Observational, retrospective cohort study performed in a third-level hospital in Spain. The population studied included patients admitted in an ED with positive blood cultures for true pathogenic microorganisms (November 2021 to June 2022). SAD was defined according to Stanford Severe Sepsis and Septic Shock Antibiotic Guide (2020), except for ceftriaxone, in which we used the recommendation of *Aaron J. Heffernan et al, 2020* (2g/24h). Data were collected on demographics, microorganisms responsible for the infection, focus of infection, antibiotics and doses used and outcomes in terms of 30-day mortality.

Results A total of 442 patients with bacteremia caused by a microorganism susceptible to the antibiotic prescribed in the ED were evaluated (Mean age: 73±15 years, 54% male), being 54 (12%) considered as SAD. From these patients, 24 infections (44%) were caused by *E.coli,* being the main focus the urinary tract (n=29, 54%). The most frequently SAD treatments were beta-lactams (n=35, 65%), followed by carbapenems (n=17, 32%), vancomycin (n=8, 15%) and aminoglycosides (n=5, 9%). Among beta-lactams, ceftriaxone was prescribed in SAD (1g/24h) in 8 patients (22%); within carbapenems, meropenem was usually prescribed (without loading dose) adjusted to kidney impairment in the moment of admission. Patients who received SAD presented a higher 30-mortality than those who received an appropriate dosing (22% vs 7%; p=0.001).

Conclusion and Relevance SAD in bacteraemic patients in the ED is 12%, being associated with higher risk of mortality. Beta-lactams and carbapenems are the most prescribed antibiotics in bacteraemia to cover gram-negative spectrum. A possible explanation for SAD in the ED might be that antibiotics are adjusted according to renal function in the moment of admission. We don't recommend adjusting doses of antibiotics during the first 24–48h of treatment in order to reduce the risk of SAD.

REFERENCES AND/OR ACKNOWLEDGEMENTS

Conflict of Interest No conflict of interest.

4CPS-054 ABSTRACT WITHDRAWN

4CPS-055 PHARMACOGENETICS AND ITS APPLICATIONS IN PERSONALISED MEDICINE: A SYSTEMATIC REVIEW

L Amaro*, J Cordero, A Martínez-Escudero, A Aguado, MÁ Calleja. *Hospital Universitario Virgen Macarena, Hospital Pharmacy, Seville, Spain*

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Background and Importance Pharmacogenetics evaluates how genetic variations influence drug responses. Nowadays, genetic tests have advanced, become more affordable, and its integration are supported by stronger clinical evidence. Guidelines such as those from CPIC and resources like PharmGKB facilitate genotype-based prescribing. Organisations like the FDA promote genetic testing before initiating certain medications. Preventive pharmacogenetic panels seems promising, but further research on biomarkers and diverse populations is needed.

Aim and Objectives This review examines recent evidence on the genotype-drug response relationship and its application in clinical practice.

Material and Methods A systematic search was conducted on PubMed to identify articles investigating the genotype-drug response relationship. The search strategy included terms such as 'pharmacogenetics,' 'personalised treatment,' 'precision medicine,' 'dose adjustment,' 'individualised dosing,' 'clinical routine,' and 'clinical practice.' Studies such as clinical trials, observational studies, and meta-analyses were included. The initial search yielded a total of 136 articles published between 2013 and 2023 for analysis.

Results 49 articles were included for the final analysis. The characteristics of the articles are explained in table 1.

A relationship between genetic polymorphisms and drug response or toxicity was found for drugs such as opioids, GLP-1 agonists, tacrolimus, oral anticoagulants, oral antineoplastics, atypical antipsychotics, efavirenz, clopidogrel, lamotrigine, anti-TNFα agents, voriconazole, SSRIs, or statins, among others. However, for drugs like metformin, quetiapine, irinotecan, bisoprolol, and anti-VEGF agents, no statistically significant association between genotype and response was found.

Conclusion and Relevance The studies analysed in this review suggest a strong correlation between genetic variability and individual drug responses, supporting the use of pharmacogenetics for treatment optimisation. However, for certain drugs like metformin, quetiapine, etc., the influence of genotype on their response remains unclear. More studies with larger sample sizes, greater ethnic diversity, and consideration of non-genetic factors are needed. Lack of standardisation in analysis methods and accessibility to genetic testing are significant challenges in this field. In summary, pharmacogenetics shows immense potential in personalised medicine, but further research is required.

REFERENCES AND/OR ACKNOWLEDGEMENTS

Conflict of Interest No conflict of interest.

Abstract 4CPS-055 Table 1

Table 1. Characteristics of studies

Study	Drug prescribed	Genotype(s) used	Primary outcome result	Study	Drug prescribed	Genotype (s) used	Primary outcome result
Abdelhady *et al.*	Efavirenz	CYP2B6*6*6	↑QTcF interval in *6/*6 carriers. CYP2B6*6*6 ↑EFV exposure.	Lee *et al.* (2018)	Clopidogrel	CYP2C19	Risk for adverse CV events was ↑ in LOF carriers.
Casajus *et al.*	Azathioprine	TPMT NUDT15	NUDT15 PMs/IMs ↑ risk of leukopenia.	Lee *et al.* (2021)	Clopidogrel	CYP2C19	PMs/IMs without *17 ↑risk of major atherothrombotic events.
Castaño-Amores *et al.*	Bisoprolol	ADRB1	ADRB1 Arg389Gly affect response to bisoprolol. Not confirmed with meta-analysis.	Limviphuvadh *et al.*	Gemcitabine	ABCG2 SLC29A3	ABCG2 Q141K CA/AA ↑ PFS and toxicity vs. CC. SLC29A3 S158F CT/TT ↑ OS vs. CC.
Cavallari *et al.* (2018)	Clopidogrel	CYP2C19	↑risk for adverse CV events in CYP2C19 IMs/PMs.	Linares *et al.*	Oxycodone	CYP2D6	Oxycodone concentrations: PM > EM > UM.
Cavallari *et al.* (2022)	Opioids	CYP2D6	CYP2D6 PMs/IMs may attain no relief from some opioids.	Lu *et al.*	Antipsychotics	CYP2D6	UMs and PMs are at increased risk for tardive dyskinesia.
Danese *et al.*	Coumarins	CYP4F2*3	CYP4F2 T allele variation needed ↑coumarin doses	Maagdenberg *et al.*	Acenocoumarol	VKORC1 CYP2C9 CYP4F2	VKORC1, CYP2C9*2/CYP2C9*3 and CYP3A4*22 ↓ stable dose.
Dapía *et al.*	Voriconazole	CYP2C19 POR CYP2C9	Contribution to interindividual variability of voriconazole AUC: CYP2C19>POR>CYP2C9.	Miroshnichenko *et al.*	Olanzapine	CYP2D6 CYP1A2	Differences were found in olanzapine concentrations in CYP2D6 PMs (G/A) and EMs (G/G).
Davis *et al.*	Cannabidiol	ADK1 SLC15A1	↑ response: ADK1 rs6729738 CC, ↓ response: SLC15A1 rs1339067 TT	Neary *et al.* (2017)	Efavirenz	CYP2B6	CYP2B6 516G>T TT ↑ EFV concentration than GG.
Dawed *et al.*	GLP-1 agonis	ARRB1 GLPR1	GLP1R Gly168Ser and ARRB1 Thr370Met ↓ HbA1c after treatment with GLP-1 agonist.	Neary *et al.* (2019)	Efavirenz	CYP2B6	Efavirenz concentration ↑ in CYP2B6 983 T>C CT vs. TT.
Degorter *et al.*	Statins	SLCO1B1 ABCG2	Rosuvastatin concentration ↑ in SLCO1B1 c.521C and ABCG2 c.421A. Atorvastatin concentrations ↑ with SLCO1B1 c.521C, ↓ with SLCO1B1 c.388G.	Ovejero-Benito *et al.* (2017)	Etanercept	HLA-B MAP3K1 PTTG1	PTTG1 rs2431697 C, HLA-B/MICA rs13437088 T ↑non-responders. MAP3K1 rs96844 C ↑ responders.
Dias *et al.*	Irinotecan	UGT1A1*28	Difference in OS, PFS between UGT1A1*28 genotypes was not statistically significant.	Ovejero-Benito *et al.* (2018)	Infliximab Adalimumab	IVL IL-12B NFKBIA	IVL rs6661932 T and NF-κB G ↑ no response. IL-12B rs2546890 A ↑ response.
Díaz-Villamarín *et al.*	Anti-VEGF	ARMS2 A69S	No statistically significant association between efficacy and ARMS2 A69S.	Packiasabapathy *et al.*	Methadone	CYP2B6	CYP2B6 PMs ↓metabolism vs. NMs. rs4803419 TT ↓ pain scores vs. CC.
Dujic *et al.*	Metformin	SLC22A1 SLC47A1	None of the variants were significantly associated with response.	Peña *et al.*	Imatinib	CYP2B6 CYP3A4	CYP2B6 G516T ↓ imatinib concentration and t1/2. ↓adverse effects in CYP3A4 *22/*22,*1/*20 and *1/*22 vs. *1/*1.
Ebid *et al.*	Tacrolimus	CYP3A4 CYP3A5	Tacrolimus levels ↑ in CYP3A4*22 and CYP3A5*3 than in CYP3A4*1 and CYP3A5*1.	Postmus *et al.*	Pravastatin	OOZ4 DNAJC5B	Not significant associations between SNPs and CV event reduction by pravastatin.
El Rouby *et al.*	Warfarin	VKORC1 CYP2C9	CYP2C9 rs4086116 T ↓ weekly warfarin dose vs. CC.	Russman *et al.*	Clopidogrel	CYP2C19	CYP2C19 IMs/PMs associated with ↓ risk of thrombotic events.
Gassó *et al.*	Fluoxetine	TPH2	rs11179002, rs60032326 and rs34517220, associated with ↑ clinical improvement.	Saiz-Rodríguez *et al.*	Clopidogrel	CYP2C19 ABCB1	CYP2C19 IM-PMs ↑ aggregation value. ABCB1 C3435T, C1236T and G2677T/A variants had ↓.
Guillat *et al.*	Apixaban	ABCG2	ABCG2 c.421C > A predictor of ↑ apixaban concentration.	Shilbayeh *et al.*	Quetiapine	CYP3A5 ABCB1	CYP3A5 *1/*1 ↑ clearance vs. *1/*3 y *3/*3.
Guo *et al.*	Warfarin	CYP2C9 VKORC1	CYP4F2*3 associated with ↑warfarin dose requirements.	Soo *et al.*	Capecitabine	TSER	TSER (TYMS enhancer region) 3R/3R ↑ tolerance to capecitabine.
Haas *et al.* (2020)	Efavirenz	CYP2B6	CYP2B6 PMs associated with ↑ plasma efavirenz.	Talamonti *et al.*	Ustekinumab	HLA-C*6	HLA-C*06 associated with ↑ and faster response.
Haas *et al.* (2021)	Rifapentine Efavirenz	NAT2 CYP2B6	NAT2 PMs ↑rifapentine concentrations. CYP2B6 PMs ↑efavirenz concentration.	Tejpar *et al.*	Irinotecan	UGT1A1	UGT1A*28 7/7 ↑ grade III-IV irinotecan-induced neutropenia.
Ham *et al.*	Benzodiazepi	CYP2C9*2/*3	CYP2C9 *2 or *3 ↑fall risk and non-carriers did not.	Theken *et al.*	NSAIDs	CYP2C9	CYP2C9 IMs/PMs ↑ NSAID exposure and risk of adverse effects.
Kato *et al.*	Fluvoxamine	5-HTTLPR FGF2	5-HTTLPR LA/S' and FGF2 rs1449683C/T associated with HAM-D change.	Thomas *et al.*	Metoprolol	CYP2D6	CYP2D6 AS=1 ↑Cl vs. AS 0. ↑HR reduction with AS 1 vs. AS 2–2.25.
Kim *et al.*	Sunitinib	ABCG2	ABCG2 421 AA associated with toxicity (thrombocytopenia, neutropenia, and HFS).	Wang *et al.*	Azathioprine	TPMT NUDT15	IMs of TPMT have increased risk of azathioprine-induced leukopenia compared with NMs.
Klarica *et al.*	Lamotrigine	ABCG2 421C>A	ABCG2 421C>A ↓ troughs of lamotrigine vs. wild-type.	Xia *et al.*	Warfarin	CYP2C9*3 VKORC1	VKORC1-1639G > A affect the most the initial dose of warfarin. The required stable dose ↑ in GG.
Zhao *et al.*	Tacrolimus	CYP3A5	Tacrolimus Cl ↑ in CYP3A5*1 vs.				