Results of a Prospective Randomised Multicentre Trial to assess the Impact of Laboratory Based Rapid Diagnostics using MALDI-TOF Technology on Outcomes of Patients with Blood Stream Infection (BSI) (RAPIDO Study)

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Blood Stream Infection: Focus on Outcome Study Group

Background

In the UK 20% of patients die within one month of diagnosis of BSI; highest mortality is with MRSA and *P.aeruginosa* (PA) bacteraemia. Due to a lack of microbiological data, broad spectrum therapy is often initially used - this may promote resistance and super infection, e.g. *C. difficile*. Rapid diagnostics can promote early appropriate narrow spectrum therapy to improve outcomes and lessen adverse events.

We used MALDI-TOF to identify BSI pathogens directly from blood cultures (BC) compared to standard practice, to assess the impact on patient mortality and a range of secondary outcomes.

Materials and methods

RAPIDO was a multicentre prospective randomised (1:1) non-blinded parallel group trial comparing MALDI-TOF and conventional microbiology (CM) to identify potential pathogens of BSI in ≥18 y receiving inpatient NHS hospital care with a bacterial or fungal BSI. Only first positive blood cultures were used. The Study was conducted in seven UK centres (Bristol, Cardiff, Leeds and London (2 centres), Newcastle and Plymouth) between July 2012 and August 2014.

The primary outcome - mortality 28 days after the BC was taken; secondary outcomes included:- 7 day mortality; time to resolution of fever; length of hospital stay (up to 28 days); incidence of *C.difficile* infection within 28 days

A Public and Patient Involvement Panel were involved with the design and delivery of the Study. The final protocol was approved by the National Research Ethics Committee South West (NRES-SW) and the National Information Governance Board (NIGB).

Table 1 : Patient demography and past history (other outcomes analysis population)

		Randomised to RAPIDO (n=2197)		Randomised to Conventional (n=2271)		Overall (n=4468)	
Demography		**n**	**%**	**n**	**%**	**n**	**%**
Males		1200/2197	54.6%	1281/2271	56.4%	2481/4468	55.5%
Age	Median (IQR) years	69.0	(55.0, 80.0)	69.0	(55.0, 80.0)	69.0	(55.0, 80.0)
Recent medical history							
Cardiac arrest up to day -7		31/2102	1.5%	36/2172	1.7%	67/4274	1.6%
Chemotherapy in last month		223/2103	10.6%	250/2172	11.5%	473/4275	11.1%
Surgery requiring overnight stay up to day -7		177/2104	8.4%	179/2171	8.2%	356/4275	8.3%
Clinical data (days -7 to 0)							
Neutrophil count at day 0 or closest [a]	Median (IQR) 10^9/L	9.2	(5.5, 13.6)	9.2	(5.3, 13.8)	9.2	(5.4, 13.7)
On ventilation at day 0		177/2078	8.5%	184/2157	8.5%	361/4235	8.5%
Temperature nearest to time0 [b]	Median (IQR) °C	38.1	(37.3, 38.7)	38.1	(37.2, 38.7)	38.1	(37.2, 38.7)
Fever present nearest to time0		1363/2013	67.7%	1416/2094	67.6%	2779/4107	67.7%
Systolic blood pressure at day 0 or closest [c]	Median (IQR) mmHg	120.5	(105.0, 140.0)	120.0	(104.0, 138.0)	120.0	(105.0, 139.0)
On IV fluids at day 0		838/2043	41.0%	946/2105	44.9%	1784/4148	43.0%
On vasopressor drugs at day 0		177/2058	8.6%	162/2140	7.6%	339/4198	8.1%
Systemic corticosteriods for shock on day 0,1 or2		99/2049	4.8%	122/2133	5.7%	221/4182	5.3%
Suspected hospital acquired infection [d]		797/2101	37.9%	794/2182	36.4%	1591/4283	37.1%
Co-morbidities at day 0							
Modified Charlson score [e]	Median (IQR)	3.0	(2.0, 4.0)	3.0	(2.0, 4.0)	3.0	(2.0, 4.0)
Cystic fibrosis		9/2101	0.4%	12/2172	0.6%	21/4273	0.5%
Mental disorientation [f]		1145/2102	54.5%	1147/2171	52.8%	2292/4273	53.6%
Any prior transplant		115/2101	5.5%	109/2170	5.0%	224/4271	5.2%
On immunosuppressive drugs at time0		242/2064	11.7%	236/2141	11.0%	478/4205	11.4%

Notes:

[a] *Data missing for 338 patients (156 RAPIDO, 182 Conventional)*
[b] *Data missing for 361 patients (184 RAPIDO, 177 Conventional)*
[c] *Data missing for 535 patients (273 RAPIDO, 262 Conventional)*
[d] *Defined as more than 2 days between admission and blood sampling*
[e] *Data missing for 1063 patients (510 RAPIDO, 553 Conventional,. 484 patients (243 RAPIDO, 241 Conventional) had a modified Charlson score of zero.*
[f] *Data also included in liver disease component of Charlson score*

Conclusions

Use of MALDI-TOF to directly identify bacteria from positive BC performed when Gram films were performed did not impact on 28 day survival or other clinical outcomes with the exception of 28 day survival for patients with PA infection.

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Results

Of the 14,298 machine positive BC, 4,312 were allocated to the intervention (MALDI-TOF ID) and 4,316 to the CM identification group. Common reasons of exclusion after allocation were ineligibility and patient retrospectively declining consent. Table 1 shows the patient demography and past medical history; Table 2 the organisms treated. The primary outcome (28 day survival) is shown in Figure 1. There was no statistically significant difference between the groups in terms of survival or hazard ratios (MALDI-TOF vs CM) 1.05, 95% CI 0.93 to 1.19, p= 0.42. Secondary outcomes are given in Table 3; except time to provision of microbiological information there were no clear differences between the groups. Figures 2 and 3 show the Sub-group analyses:- clinical significance and pathogens. There was a suggestion of reduced mortality associated with MALDI-TOF for the subgroup of patients with PA infection.

Table 2: Organism by treatment allocation

	Randomised to RAPIDO (n=2197)		Randomised to CM (n=2271)		Overall (n=4468)	
	n	%	n	%	n	%
CNS	616	28.0	611	26.9	1227	27.50%
E. coli	439	20.0	481	21.2	920	20.60%
MSSA	165	7.5	165	7.3	330	7.40%
K.pneumoniae	76	3.5	83	3.7	159	3.60%
S. pneumoniae	56	2.5	82	3.6	138	3.10%
P. aeruginosa	55	2.5	59	2.6	114	2.60%
Corynebacterium spp	37	1.7	34	1.5	71	1.60%
P. mirabilis	27	1.2	35	1.5	62	1.40%
E. cloacae	22	1.0	35	1.5	57	1.30%
MRSA	28	1.3	25	1.1	53	1.20%
Other single organism	508	23.1	510	22.5	1018	22.80%
Polymicrobial	168	7.6	151	6.6	319	7.10%

Figure 1: Kaplan-Meier curve for 28-day mortality

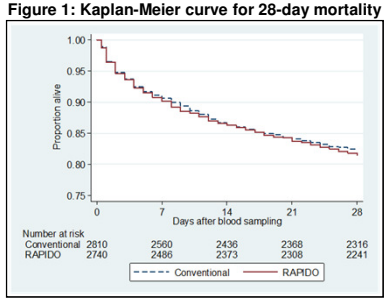
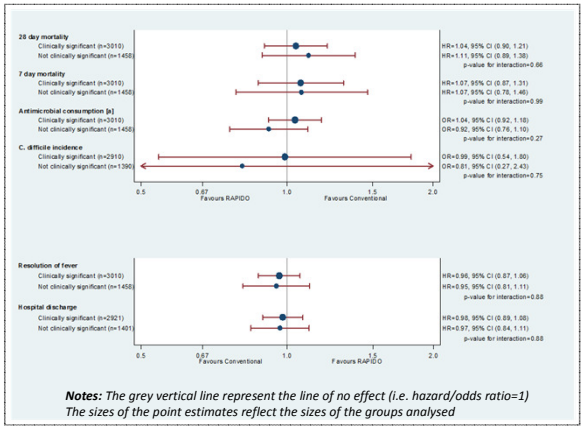


Table 3: Secondary outcomes

		Randomised to RAPIDO (n=2740)		Randomised to Conventional (n=2810)		Estimate [a] (95% CI)	p-value
Mortality outcomes		**n**	**%**	**n**	**%**		
Seven day mortality		9.9%		9.3%		HR=1.05 (0.89, 1.25)	0.54
Other outcomes (excluding unapproached survivors)		**Randomised to RAPIDO (n=2197)**		**Randomised to Conventional (n=2271)**		**Estimate [a] (95% CI)**	**p-value**
Antimicrobial consumption (total defined daily doses) over first 7 days	Median (IQR)	8.0	(4.3, 14.3)	7.8	(4.4, 14.0)	OR=0.98 (0.89, 1.09)	0.73
C. difficile incidence (28 days)		27/2114	1.3%	30/2186	1.4%	OR=0.94 (0.55, 1.58)	0.81
Time to provision of microbiological identity	Median (IQR) hours	35.6	(25.3, 45.3)	54.5	(46.9, 69.5)		<0.0001
Gram stain result to ward	Median (IQR) hours	32.1	(23.5, 43.2)	30.5	(23.3, 42.0)		
MALDI ID to ward	Median (IQR) hours	35.6	(25.3, 45.3)				
Provisional or Final ID to ward	Median (IQR) hours			54.5	(46.9, 69.5)		
Antimicrobial susc. data to ward	Median (IQR) hours	54.0	(45.9, 69.9)	55.2	(46.9, 72.3)		
Time to resolution of fever (↑7 days)	Median (IQR) days	3	(1, 5)	3	(1, 5)	HR=0.96 (0.88, 1.04)	0.32
Time to hospital discharge ↑ 28 days)	Median (IQR) days	15	(7, -)	15	(7, -)	HR=0.98 (0.90, 1.06)	0.55
De-escalation of broad-spectrum antimicrobial therapy (↑ 7 days)	Proportion on broad-spectrum therapy at 7 days		82.7%		84.2%	HR=1.10 (0.90, 1.36)	0.35

Figure 2: Subgroup analyses by clinical significance (primary and secondary outcomes)



Notes: The grey vertical line represent the line of no effect (i.e. hazard/odds ratio=1) The sizes of the point estimates reflect the sizes of the groups analysed

Figure 3: Subgroup analyses by BSI (primary outcome only)