Figure 1 Absolute difference plot (A): absolute difference between creatinine clearance test (CCT) and estimated glomerular filtration rate (eGFR) plotted against the Mean of the creatinine clearance and eGFR. Percentage difference plot (B): percentage difference between creatinine clearance and eGFR plotted against the Mean of the creatinine clearance and eGFR. Difference in GFR with increasing proteinuria (C): percentage difference between creatinine clearance and eGFR plotted against the daily urinary protein.

Table 1 Relationship between proteinuria and the median percentage difference between creatinine clearance and estimated glomerular filtration rate

Proteinuria (g/day)	Number	Median % difference
<0.02	13	51.1
0.02–0.19	25	39.3
0.20–0.49	11	32.3
0.5–0.99	14	39.8
1.0–2.99	13	50.8
≥3.0	9	38.4
Unknown	15	41.8

between two or more of the medians of the five CKD stages. Also expected is the increased difference in the absolute difference with the increase in the GFR; however, the percentage difference plot shows no evidence of an increase in the range of individual values with increasing GFR, especially >60 ml/min/ 1.73 m².

Despite the problems with the CCT, it is still the method routinely used in the determination of GFR, with many patients being incorrectly classified as a result. Compared with the CCT, it is to be expected that eGFR will result

in fewer misclassifications despite issues such as analytical interference, imprecision and calibration. The user-friendly four-variable MDRD-derived eGFR overcomes the positive bias of the CCT across all stages of CKD and degrees of proteinuria when using the Olympus kinetic alkaline picrate assay. Accordingly, we believe that the four-variable MDRD-derived eGFR should be reported instead of the CCT across all stages of CKD.

Patrick J Twomey, Derek R Pledger

Department of Clinical Biochemistry, The Ipswich Hospital, Ipswich, Suffolk, UK

Correspondence to: Dr P J Twomey, Department of Clinical Biochemistry, The Ipswich Hospital, Health Road, Ipswich, Suffolk IP4 5PD, UK; taptwomey@aol.com

doi: 10.1136/jcp.2005.033472

Accepted 20 November 2005

Competing interests: None declared.

References

- Burton PR, Walls J. Selection-adjusted comparison of life-expectancy of patients on continuous ambulatory peritoneal dialysis, haemodialysis, and renal transplantation. *Lancet* 1987;1:1115–19.
- Jungers P, Zingraff J, Albouze G, et al. Late referral to maintenance dialysis: detrimental consequences. *Nephrol Dial Transplant* 1993;8:1089–93.
- Arora P, Obrador GT, Ruthazer R, et al. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 1999;10:1281–6.
- Pereira BJ. Optimization of pre-ESRD care: the key to improved dialysis outcomes. *Kidney Int* 2000;57:351–65.
- National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification, part 5. Evaluation of laboratory measurements for clinical assessment of kidney disease. http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p5_lab_g4.htm (accessed 14 Mar 2007).
- The Renal Association. UK CKD guidelines. <http://www.renal.org/CKDguide/full/UKCKDfull.pdf> (accessed 14 March 2007).
- Department of Health. The national service framework for renal services. Part two: chronic kidney disease, acute renal failure and end of life care. http://www.regenstrief.org/medinformatics/loinc/meetings/20040312/laboratory-loinc-meeting-03-12-2004/handout-h3_1.pdf (accessed 4 April 2007).
- National Kidney Foundation. Frequently asked questions about GFR estimates: <http://www.kidney.org/kls/patients/faq.cfm> (last accessed 7 Jun 2005).
- Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–70.
- Walpole RE, Myers RH. Probability and statistics for engineers and scientists. 2nd edn. New York: MacMillan, 1978.
- Method validator Philippe Marquis. <http://www.marquis-soft.com/> (accessed 14 Mar 2007).
- Lawson N, Lang T, Broughton A, et al. Creatinine assays: time for action? *Ann Clin Biochem* 2002;39:599–602.

Over 18 h to positivity in the Bact/ALERT system with clustered Gram-positive cocci is highly predictive of coagulase-negative staphylococci

Coagulase-negative staphylococci (CoNS) are the most common bacteria isolated from blood cultures, but a great proportion of them are most likely contaminants.^{1,2} On the other hand, one single positive blood culture for *Staphylococcus aureus* is usually sufficient to diagnose bacteraemia. Therefore, a rapid method of differentiating CoNS from *S aureus* would assist in the clinical decision on starting antimicrobial treatment in a timely manner. As many laboratories routinely process blood culture bottles in automated systems that record time to positivity (TTP) and this information is readily available along with the Gram-smear results, we assessed the

Table 1 Proportion of patients with the first positive bottle in each time interval

Time to positivity (h)	No. of patients with first positive bottle			p Value
	<i>S aureus</i>	CoNS	Total	
≤13.0	27 (19.3)	11 (1.2)	38	<0.01
13.1–14.9	25 (17.8)	17 (1.9)	42	<0.01
15.0–17.9	40 (28.6)	57 (6.4)	97	<0.01
≥18.0	48 (34.2)	805 (90.5)	853	<0.01
Total	140	890	1030	

CoNS, coagulase-negative staphylococci; *S aureus*, *Staphylococcus aureus*.
Values in parentheses are percentages.

Table 2 Positive predictive values for *Staphylococcus aureus* and coagulase-negative staphylococci in each time interval

Time to positivity (h)	Predictive value (%) / LR for		p Value
	<i>S aureus</i>	CoNS	
≤13.0	71/15.8	28/0.063	<0.01
13.1–14.9	59.5/8.9	40/0.10	<0.01
15.0–17.9	41/4.6	58/0.22	<0.01
≥18.0	5.6/0.37	94/2.6	<0.01

CoNS, coagulase-negative staphylococci; LR, likelihood ratio; *S aureus*, *Staphylococcus aureus*.

predictive value of TTP for the exclusion of *S aureus* in the setting of a positive result for clustered Gram-positive cocci.^{1 3 4}

Methods

For this purpose, we retrospectively analysed all blood cultures collected from patients between January 2005 and February 2006 in a large university teaching hospital. In our hospital, we routinely collected two blood cultures for every patient, each one consisting of a single BacT/ALERT FA aerobic bottle. The sets were incubated in the BacT/ALERT 240 system (Organon Teknika, Boxtel, The Netherlands). A routine Gram-stain microscopic examination was performed whenever bacterial growth was detected. The TTP was recorded in the software system. The definitive identification of staphylococci relied on the tube coagulase test, which is usually available only overnight. We included only the first positive bottle from each patient in the analysis, because this is the moment when the clinical decision to initiate antibiotic treatment is made. TTP was grouped in the following time intervals: ≤13 h, from 13.1 to 14.9 h, from 15 to 17.9 h and >18 h (table 1). The positive predictive value (PPV) and the likelihood ratios (LRs) for the presence of *S aureus* or CoNS for each time interval were then calculated (table 2).

Results

A total of 18 479 blood culture samples were collected between January 2005 and February 2006. We found 1030 isolates of staphylococci, of which 140 (13.6%) were identified as *S aureus* and 890 (86.4%) as CoNS (table 1). The PPV for *S aureus* was 71% for isolates growing in ≤13.0 h of incubation (LR 15.8). In the same time interval, however, only 28% of positive isolates were characterised as CoNS (LR 0.063). At the opposite extreme (≥18 h), the PPV for *S aureus* fell to 5.6% (LR 0.37), whereas for CoNS, the PPV was 94% (LR 2.6; table 2).

Discussion

The demonstration of clustered Gram-positive cocci in the direct blood examination constitutes a common clinical dilemma.^{1 4} As the majority of the isolates will eventually be revealed to be CoNS, systematic initiation of early empirical anti-Gram-positive treatment would not be warranted because of cost, toxicity and selective pressure issues.⁵ On the other hand, even minimal delays in starting appropriate treatment could be deleterious in the case of true bacteraemia due to *S aureus*. Therefore, a rapid method of accurate differentiation between *S aureus* and CoNS would be of great clinical importance.^{1 3 4 6} Oliveira *et al*³ described a method of direct identification using fluorescence in situ hybridisation, which was both sensitive and specific for species differentiation. However, the test required up to 2.5 h of preparation and was not cost free. Murdoch and Greenlees⁸ described a method for identification based on direct Gram-stain characteristics, such as the size of the bacterial cells and the number of cells in a typical cluster. However, the method requires expertise and may not be feasible in a large tertiary care centre that processes a great number of samples. Ruimy *et al*⁷ recently showed that the TTP, which is automatically recorded by automated systems, could be used for rapid identification. Using the BACTEC 9240 System (Becton Dickinson Diagnostic Instrument Systems, Sparks, Maryland, USA), the authors found a PPV of 83% for *S aureus* when the TTP was from 2 to 9 h and a PPV of 91% for CoNS when positivity occurred beyond 18 h of incubation. We theorised that this also would apply for the BacT/ALERT 240, as this system is associated with a higher mean detection time than the BACTEC 9240.^{7 8}

In summary, to our knowledge, there are no previous studies analysing the performance of TTP using BacT/ALERT 240. Our results support the notion that the TTP is also a useful tool while using the BacT/ALERT 240. In particular, we suggest that clinicians should not routinely initiate empirical anti-Gram-positive treatment

when the first bottle displays clustered Gram-positive cocci after >18 h of incubation. In this setting, the very high PPV for CoNS permits deferring treatment until the results of the second bottle are known. Because of the low virulence of CoNS, the delay to starting antimicrobial treatment does not jeopardise the clinical outcome in cases of true bacteraemia. In addition, a great deal of unnecessary empirical treatment would be avoided in the hospital setting.

Ricardo A Zimerman, Denise P Machado,
Caroline C Constante, Afonso L Barth,
Luciano Z Goldani

Section of Infectious Diseases and Microbiology Unit,
Hospital de Clínicas de Porto Alegre, Universidade
Federal do Rio Grande do Sul, Porto Alegre, Brazil

Correspondence to: Dr L Z Goldani, Serviço de
Infecologia, Hospital de Clínicas de Porto Alegre,
Ramiro Barcelos 2350, 900035-003, Porto Alegre, RS,
Brazil; lgoldani@ufrgs.br

doi: 10.1136/jcp.2006.045641

Accepted 26 January 2007

Published Online First 13 February 2007

Competing interests: None declared.

References

- Chapin K, Musgnug M. Evaluation of three rapid methods for the direct identification of *Staphylococcus aureus* from positive blood cultures. *J Clin Microbiol* 2003;**41**:4324–7.
- von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase negative staphylococci. *Lancet Infect Dis* 2002;**2**:677–85.
- Oliveira K, Brecher SM, Durbin A, *et al*. Direct identification of *Staphylococcus aureus* from positive blood culture bottles. *J Clin Microbiol* 2003;**41**:889–91.
- Ruimy R, Lefevre A, Andrement A. Short time to positivity in blood culture with clustered Gram-positive cocci on direct smear examination is highly predictive of *Staphylococcus aureus*. *Am J Infect Control* 2005;**33**:304–6.
- Paul M, Borok S, Fraser A, *et al*. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2005;**55**:436–44.
- Murdoch DR, Greenlees RL. Rapid identification of *Staphylococcus aureus* from BacT/ALERT blood culture bottles by direct Gram stain characteristics. *J Clin Pathol* 2004;**57**:199–201.
- Endimiani A, Tamborini A, Luzzaro F, *et al*. Epidemiology of bloodstream infections and time to detection of positive blood cultures: an evaluation of the automated BacT/ALERT and BACTEC 9240 systems. *New Microbiol* 2002;**25**:9–16.
- Vigano EF, Vasconi E, Agrappi C, *et al*. Use of simulated blood cultures for time to detection comparison between BacT/ALERT and BACTEC 9240 blood culture systems. *Diagn Microbiol Infect Dis* 2002;**44**:235–40.