The hidden killer: are we improving the management of bacteremia?

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Advances in medicine are accompanied by an ascending toll of infectious complications. In a previous thematic section we reviewed the burden of bacteremia, as a marker of severe infections [1]. A population-based incidence rate of bacteremia ranging between 140 and 160 per 100 000 in high-income countries was compiled from many studies, making the burden of bacteremia alone comparable to diseases such as major stroke, acute myocardial infarction and trauma [2]. In a systematic review of population-based studies, bacteremia came out as the fifth to seventh leading cause of death in North America and several countries in Europe [3]. Although not counted separately in the Global Burden of Disease, bacteremia mortality rates of 23.5 to 27.5 per 100 000 person-years in the USA, bring it above most age-standardized death rates for individual conditions [4]. Nosocomial bacteremias affect between 2.7 and 8.2 of patients admitted to hospitals in the USA and Europe, with short-term mortality rates ranging between 12 and 32% of patients [3]. Consequences of bacteremia extend well beyond the first month after infection, with curtailed long-term survival, impairment in quality of life, cognitive function and functional capacity [5].

The current theme issue addresses contemporary clinical and microbiological tools for improving the management of bacteremia. Rates of appropriate empirical antibiotics for patients with bacteremia have not improved with time, but rather decrease with increasing antimicrobial resistance [6,7]. We need tools to identify infections early on and prescribe covering and effective antibiotics to those with severe bacterial infections. We need to avoid unruly empirical antibiotics for patients who do not have severe infections and to avoid antibiotic treatment altogether in those who do not have a bacterial infection. Empirical data showing lower mortality associated with early covering antibiotics are restricted to patients with severe infections, mostly with bacteremia [8]. By definition data are restricted to patients with microbiologically documented infections. Implementing the evidence for all patients with suspected infection results in high rates of unnecessary antibiotics. We need better triage of patients with severe bacterial infections and point-of-care tests for prescribing appropriate and non-superfluous antibiotics to these patients. Here, we address the promises and disappointments of contemporary research into improving bloodstream infection diagnosis and management.

Eliakim-Raz *et al.* reviewed prediction models for bacteremia [9]. On the whole, the models performed well. Starting usually with non-selected patients from whom blood cultures were drawn, the models could triage patients into substantially sized low-risk and high-risk groups. In the low-risk group the median percentage of patients with bacteremia was 2.7% in the derivation cohorts and 2.9% in the validation cohorts (range 0–15%). In the high-risk group bacteremia rates were 35% (range 14–83%) in the derivation cohorts and 28.5% (range 11–80%) in the validation cohorts. This compares favourably with physicians' performance, which was formally assessed in a single study and a single centre and reported that physicians markedly overestimated the probability of bacteremia (physicians' prediction of 16–40% versus actual 4.2%; and physicians' prediction of 41–99% versus actual 12.2%) [10]. However, none of the bacteremia prediction studies compared the suggested model to physicians' performance directly and none were tested in an interventional clinical study to examine the effects of the model on patient outcomes, except for a single model that was tested as part of a more complex decision support system [11]. Furthermore, through correspondence with the primary model developers, the authors established that none of these models are being used in clinical practice. Hence, prediction models for bacteremia hold promise but have not been ingrained into clinical practice.

Pogue *et al.* review methods to improve appropriate empirical antibiotic treatment in the era of multidrug-resistant

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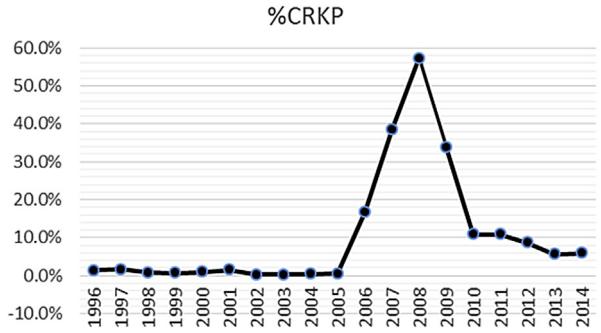

FIG. 1. Rates of carbapenem-resistance of all *Klebsiella pneumoniae* clinical isolates, at Rambam Health Care Campus between 1996 and 2014.

(MDR) bacteria [12]. Unlike the bacteremia prediction models, the models attempting to predict infections caused by MDR bacteria do not perform particularly well. The authors present selected models with sensitivity values ranging from 44 to 86% and specificities from 41 to 98%, where models with good sensitivity have poor specificity and vice versa. Difficulties encountered in such models include 'resistance-specific' risk factors that are shared among different MDR species and 'species-specific' risk factors shared between antibiotic-susceptible and antibiotic-resistant phenotypes of the same species. Furthermore, implementation of these models requires that the control population in the original studies mimic the patient population suspected of infection in clinical practice, which was not the case with most studies to date. To be useful in directing antibiotic prescription, the models should predict both the existence of a severe infection and the MDR phenotype. Finally, perhaps the greatest difficulty with such models is that a model is relevant to a specific epidemiological setting. Even in the same locale the model cannot remain fixed for long because there is an epidemic curve of new resistance traits that depends on many factors. As an example, the epidemic curve of carbapenem-resistant *Klebsiella pneumoniae* in one hospital is shown in Fig. 1 (personal data). A model developed in 2008 in response to the carbapenem-resistant *Klebsiella pneumoniae* outbreak would probably not be relevant a year later. As in the bacteremia prediction models, the models to predict MDR bacteria have not been adopted into clinical practice to date.

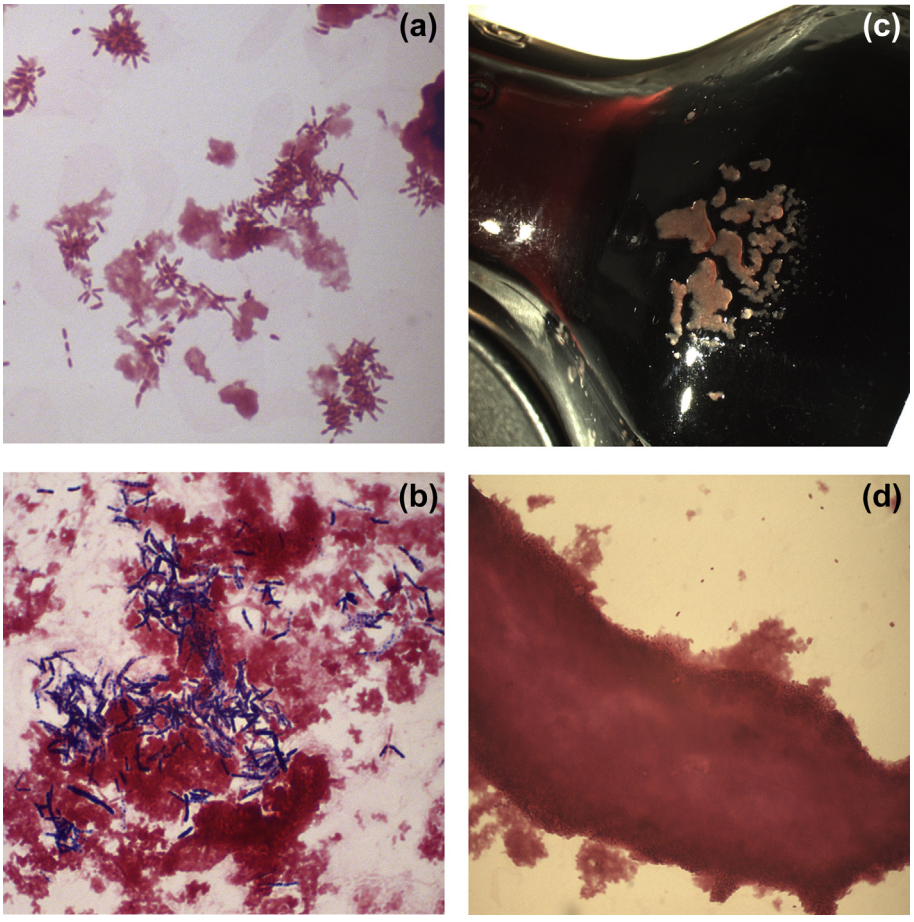

FIG. 2. Usefulness of Gram staining of positive blood cultures for presumptive early bacterial identification. (a) Gram stain of a blood culture broth positive for *Cardiobacterium hominis* showing typical pleomorphic Gram-negative bacilli arranged as rosettes or presenting teardrop forms; the patient presented a prosthetic endocarditis. (b) Gram stain of a positive blood culture pellet showing the typical aspect of mycobacteria with heterogeneous Gram-positive staining. (c) Brown granules macroscopically visualized in a positive anaerobic blood culture bottle taken from a patient suffering from *Aggregatibacter actinomycetemcomitans* endocarditis. (d) Gram stain of the blood culture bottle shown in (c), showing the huge granules resulting from the aggregation of *Aggregatibacter actinomycetemcomitans*, a bacterium named based on its adhesive properties. (Pictures kindly provided by G Prod'hom, Lausanne, Switzerland.)