To Screen or Not to Screen? The Problem of Resistant Gram-Positive and Gram-Negative Bacterial Pathogens

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Abstract

Parallel to the use of antimicrobials in medicine, resistance in bacterial pathogens evolved. With the introduction of penicillin in medicine, resistance in Staphylococcus aureus increased, first in hospital acquired strains and later in community acquired strains. A similar development was observed after methicillin therapy started in 1961, with a steep increase of prevalence of methicillin resistant S.aureus strains (MRSA) thirty years later. Besides MRSA, now resistance in Gram-negative bacteria is of great concern. Antibiotic stewardship programs, improvements in hospital hygiene and screening are tools to fight against the threat of a post antibiotic era.

General screening of patients admitted to hospitals to detect multiresistant bacteria leads to a significant reduction of hospital acquired infections and also to an improved patient management especially early appropriate antibiotic therapy which leads to decreased mortality and shorter length of stay. Fast and reliable laboratory methods to detect multi resistant bacteria are crucial. Detection of resistance genes by DNA amplification is fast but relatively expensive and may also have some pitfalls. Culture based methods on the other hand may need too much time, however they are less costly. A new developed method based on liquid culture with selective supplements and detection of growth by laser light scattering offers a new, sensitive and cost saving opportunity.

INTRODUCTION

The worldwide emergence of multi resistant bacteria is presently and in the future one of the major challenges in medicine. In this paper an overview of development of resistance with emphasis on S.aureus; the rationale for screening and also the latest development in laboratory methods is given.

EPIDEMIOLOGY

In 1929 Alexander Fleming published his Nobel Prize (1945) winning experiments on the antibacterial action of penicillum [1]. However; the first antibacterial substances in clinical use were sulphonamides developed by Gerhard Domagk (Nobel Prize 1939) [2]. In the same year as penicillin was introduced as a chemotherapeutic agent [3]; an enzyme produced by Escherichia coli able to destroy penicillin (ß-lactamase) was described [4]. Shortly after that time;the increase of penicillin-resistance conferred by ß-lactamases started in S.aureus strains isolated from hospitalized patients raising to a level of approximately 80% in the mid fifties. The same was observed for strains detected outside the hospital with a delay of around 15 years [5]. The Time Magazine from March 24th; 1958 published the following statement: „ Sulfa drugs and antibiotics have worked miracles against most kinds of germs; but one species; Staphylococcus aureus; their too-liberal use has backfired. Last week US physicians were pondering massive evidence in the A.M.A. Journal showing that i) infections acquired in hospitals are a deadly and growing peril; and ii) antiseptic methods are as important as ever.“ This statement holds true even nearly 60 years later. To overcome penicillin-resistance; new ß-lactamase stable penicillin derivatives were synthesised (methicillin; called “celbenin”) and introduced in clinical practice in 1961. But in the same year also the first MRSA strains were detected [6] and an editorial warned: “They are exceedingly rare; but the more unpleasant strains of this organism have a diabolical capacity for persistence and spread” [7]. Several years later a new headline of the Time Magazine from August 31st; 1992 stated: “Revenge of the killer microbes. Are we loosing the war against infectious diseases?” Again; S.aureus was in the scope of interest; because a dramatic raise of hospital acquired MRSA strains (HA-MRSA)
measurements may also help in situations after an outbreak of resistant strains was not found to be necessary. A study done in outbreak over at least three years in a neonatology intensive care "at risk" for MRSA were screened. Another example is an ESBL-further actions; e.g. hand hygiene or a bundle of additional mentioned that screening always has to be seen in relation to infections (RR: 0.69; CI: 0.46-1.01) [25]. However; it has to be in infections (RR: 0.54; CI: 0.41-0.71) and also surgical wound or transmission rates were found for MRSA blood stream [24].

of a MRSA bundle including screening of nasal swabs a significant [14] and also Acinetobacter baumannii [15,16] belonging mainly to Ambler class A (e.g. KPC 1-3); D (e.g. OXA-48) and also B (metallo-ß-lactamases e.g. VIM). An overview on the changing situation of resistance in Europe was recently published [17]. One of the risk-factors driving resistance in Gram-positive as well Gram-negative bacteria is antibiotic consumption in general as well as preceding application in individual patients [18,19]. Main factors for selection of MRSA but also for ESBL-producing Enterobacteriaceae seem to be fluoroquinolones and 3rd generation cephalosporins [20-22]. Driving forces of carbapenem resistance and risk factors are occurrence of ESBL-producing bacteria in a hospital and prior administration of 3rd, 4th generation cephalosporins (OR 27.96; p<0.001) [23].

Rationale to Screen

As a result of the Veterans Affairs initiative to prevent methicillin-resistant S. aureus infections the full implementation of a MRSA bundle including screening of nasal swabs a significant reduction of health care associated MRSA infections (p<0.001) was observed in patients treated in ICUs as well as in non-ICUs [24].

In a meta-analysis in 27 out of 36 investigations with compulsory MRSA screening decreasing rates of MRSA infections or transmission rates were found for MRSA blood stream infections (RR: 0.54; CI: 0.41-0.71) and also surgical wound infections (RR: 0.69; CI: 0.46-1.01) [25]. However; it has to be mentioned that screening always has to be seen in relation to further actions; e.g. hand hygiene or a bundle of additional measures. Inconsequent screening results in so called silent epidemics. Even in countries claiming to fight MRSA by a "search and destroy" policy; such silent epidemics seem not to be so rare [26, 27]. The reason for this is that obviously only patients “at risk” for MRSA were screened. Another example is an ESBL-outbreak over at least three years in a neonatology intensive care unit in Germany [28]; because screening or documentation of resistant strains was not found to be necessary. A study done in 26 long-term care facilities (Germany) disclosed that in nearly all residents with positive screening for MRSA and ESBL the carriage had not been known before [29]. Screening including a bundle of measurements may also help in situations after an outbreak of carbapenemase-producing Enterobacteriaceae as could be shown in an Italian study [30].

Since two years at least in Europe a new epidemiological situation emerged through uncontrolled mass immigration of refugees from the Near East and from Africa north of the equator. In this geographical regions multi resistant pathogens (MRSA; ESBL and carbapenemase-producing bacteria) are widely distributed in the population [31-38]. In two studies from Germany [39,40] the prevalence of ESBL-producing bacteria in refugees (Near East; Africa) was 35% compared to 7.5% in the indigenous population. Refugee patients admitted to Frankfurt University Hospital were also positive for ESBL-producing bacteria in 60.8% compared to 16.7% non-refugee patients and for MRSA in 5.6% compared to 1.2% in non-refugees. If undetected; the risk of silent spread of multi resistant bacteria in the whole population will probably increase.

Patients infected by resistant bacteria have a higher risk to die; a shorter time to death or a longer hospital stay compared to patients with infections caused by sensitive strains [41-45]. In general; patients with severe infections e.g. bloodstream infections caused by Gram-negative pathogens have a lower probability of 28-day mortality receiving appropriate antimicrobial therapy [46]. It is now well accepted that early adequate antimicrobial therapy is crucial for the outcome of infections caused by bacterial pathogens. Several study groups showed that mortality was reduced in patients receiving adequate initial antibiotic therapy [47-51]. Lack of response to initial medical treatment is an independent determinant of hospital mortality [52]. However; the chance to receive appropriate antimicrobial therapy in patients with infections due to multiresistant bacteria is significantly less in cases where colonization was unknown before [53,54]. On the contrary it is possible to predict e.g. methicillin resistance in a culture-positive clinical infection with S.aureus when a screening swab was obtained on same admission or within 48 hours before collection of the clinical isolate [55].

Consequently; as a result of screening there are at least three benefits:i) knowing a patient is colonized by a multiresistant pathogen can guide the choice of antibiotic leading to a higher chance for appropriate initial therapy; ii) precautions can be taken early to avoid the spread of multi resistant bacteria within an institution and iii) better knowledge of the epidemiology of multi resistant bacteria in the population.

METHODS

In principle there are two methods for screening; the one is PCR-based detection of genes coding resistance and the other culture-based (phenotypical detection). PCR tests are now widely distributed because it is claimed that these tests are simple to use; fast; sensitive and specific. Besides the fact that mutations of the genome will probably not be detected by amplification methods it is worth to have a closer look on the reality. One popular system is the BD MAX (Becton Dickinson; USA); according to the package insert (accessed 3.11.2016) sensitivity of the test add up to 93%; specificity 95.9%; but the positive predictive value (PPV) is 67% (total of 217 positive results by BD MAX including 71 false positive results compared to the reference method). In a recently published evaluation of the BD MAX a sensitivity
of 80%; a specificity of 90% and a PPV of only 17% was found. Another crucial point was the number of inhibited samples (12/216) [56]. The second system is GeneXpert MRSA (Cepheid; USA) with a sensitivity of 86.3%; a specificity of 94.9% and a PPV of 80.5% according to the product information (accessed 3.11.2016). However; field studies are mirroring a different scenario. In a population of patients with a MRSA prevalence of 3% 1891 patients admitted to a hospital (Brussels; Belgium) MRSA screening was done using GeneXpert compared to culture: GeneXpert sensitivity was 60%; specificity 97%; PPV 93%; specificity of 97.9% and a PPV of 79.8% [57]. In a recently published very small study; the performance of GeneXpert Gen3 and BD MAX XT were compared to culture with sensitivities of 95%; 7% and 97.5%; specificities of 100% and 97.1% and PPVs of 100% and 93.3% respectively [59].

Culture based methods are still the gold standard; but may need up to 72 hours for final results. During that period of time the chance of transmission from the unknown positive patient without contact isolation to other patients is increasing. On the other side phenotypic detection of resistance has the chance to detect also mutants and; not unimportant; the costs for testing are quite low.

To overcome the problems of phenotypic methods; a new test method was developed by ALIFAX (Italy). The samples (e.g. nose and throat for MRSA) are transferred to a liquid medium with selective supplements for detection of MRSA; ESBL- and carbapenemase-producing bacteria and incubated in a semi-automated instrument (HB&L) or in a fully automated device (ALFRED). Within 75-8 hours growth kinetics are detected by laser light scattering and interpreted by an internal algorithm of the software. Evaluation of this system for rapid detection of intestinal carriage of carbapenemase-producing Enterobacteriaceae resulted in a sensitive method (61%; 2% after 4 hours; 83.5% after 20 hours) compared to direct plating on chromogenic medium (74.2%; after 20 hours) and reference method by CDC (96.8% after 72 hours) [60]. In a field study we are now comparing the performance of the HB&L MRSA test with culture on chromogenic agar and an automated PCR method.

CONCLUSIONS

In the light of changing patterns of emergence of resistant bacteria and of epidemiological situations compulsory screening for MRSA; ESBL and carbapenemase positive bacteria are urgently needed in terms of patient care and hospital hygiene. Ideally the screening method should have a short turn around time as well as a high sensitivity; specificity and PPV. One also has to take into account the increasing costs with broad testing. Probably a method like HB&L; which is at least comparable to PCR and culture; combines all requirements needed.

CONFLICT OF INTEREST

W R Heizmann received honoraria from Bayer (Germany); Pfizer (Germany; France); ALIFAX S.A. (Italy).

REFERENCES


