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EDITORIAL

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Maximizing rates of empiric appropriate antibiotic therapy with minimized use of broad-spectrum agents: are surveillance cultures the key?

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Of the many therapeutic decisions, physicians have to face in daily ICU practice choosing initial antibiotic therapy in the patient with suspected severe nosocomial sepsis is one of the more challenging. To favourably impact the outcome, antibiotic therapy covering the offending pathogen has to be initiated without delay [1, 2], which implies administration within 24 h of clinical deterioration and within 1 h of septic shock. This therapeutic choice is little supported by the microbiology lab, as microbiological identification and susceptibility testing usually require 48 h. In patients at risk for infection with multidrug resistant (MDR) pathogens, the clinician has to resort to broad-spectrum antimicrobials, which are themselves linked with the emergence of multidrug resistance. In this respect, appropriate empirical antibiotic therapy should have a balanced antimicrobial spectrum that includes the susceptibility of the infectious pathogen, but does not add unnecessary selection pressure. As the prevalence and complexity of MDR patterns steadily rise, finding this balance is increasingly difficult. Therefore the empirical use of broad-spectrum antibiotic drugs in patients at risk for MDR pathogens is advocated [3, 4], meeting the need to restrict antimicrobial selection pressure by promoting subsequent de-escalation guided by culture results.

As an alternative to empirical combination antibiotic therapy, a more focused initial antibiotic selection guided by surveillance cultures (SC) has been reported. This strategy rests upon the observation that invasive disease by typically nosocomial (and potentially MDR) pathogens is preceded by colonization of such easy to sample anatomical sites as the gut and the oropharynx, the lower airways and catheter insertion sites [5]. In order to be of clinical use in directing initial antibiotic therapy, SC must be able to detect this colonization rapidly and with high sensitivity, as false negative results would place the patient at risk for inappropriate therapy. Moreover, a focused antibiotic choice, with limitation of unnecessary broad-spectrum drugs, requires a low number of false positive surveillance results.

In this journal, two publications contribute to the test characteristics of SC as predictors of MDR infectious etiology. Papadomichelakis et al. [6] found SC to have good positive predictive values (67–94%) and negative predictive values (73–100%) for ventilator-associated pneumonia (VAP) caused by *Acinetobacter*, *Pseudomonas* or *Klebsiella* species. For bacteremia caused by these microorganisms, positive predictive values were low (43–54%), while negative predictive values remained high (88–100%). Consequently, surveillance-guided initial antibiotic therapy was appropriate in 91 and 86% of patients with VAP and bacteremia, respectively. However, in patients without detected colonization the rate of appropriate therapy was unacceptably less than one to two. These data are in favour of surveillance-assisted empiric therapy in a setting with a high prevalence of MDR, albeit that the local MDR problem was insufficiently appreciated in the absence of individual surveillance results. The historical cohort study by Jung et al. [7] examined concordance between microbial etiology of VAP and preceding tracheal aspirates. Surveillance results (available in 80% of patients) were concordant with VAP etiology in 72% but discordant in 28% of the cases. The

Table 1 Overview of studies reporting concordance between surveillance culture results and etiology of nosocomial infections

Author (reference no.)	Type of infection	Number of episodes, *n*	Surveillance technique	Sampling frequency	Surveillance cultures available, *n* (%)	Percentage predicted etiology[a]
Papadomichelakis E et al. [6]	VAP caused by gram-negative bacilli	31	Tracheal aspirates Rectal swabs	2/week 1/week	28 (90)	69% (Aspirates) 58% (Rectal swabs) 82% (all cultures)
Jung B et al. [7]	VAP	113	Tracheal aspirates	1/week	90 (80%)	72%
Hayon J et al. [12]	VAP	125	Respiratory tract samples[b] Nasal swab Rectal swab Urine culture	On indication 1/week 1/week 1/week	102 (82)	35% (Respiratory tract) 16% (All cultures)
Bouza E et al. [5]	VAP Trachea-bronchitis	28 29	Respiratory tract samples[c]	1/week	28 (100) 29 (100)	4% 4%
Delclaux C et al. [19]	VAP in ARDS patients	24	Respiratory tract samples[d]	2–3/week	24 (100)	66%
Malacarne P et al. [16]	Late onset *Acinetobacter baumannii* VAP	20	Tracheal aspirates	2/week	20 (100)	90%
Boots RJ et al. [15]	VAP	58	Low-volume mini BAL	3/week	58 (100)	85%
Michel F et al. [11]	VAP	41	Tracheal aspirates	2/week	40 (98)	85%
Depuydt P et al. [9]	Bacteremic pneumonia	128	Tracheal aspirates	3/week	110 (86)	61%
Depuydt P et al. [10]	Bacteremic pneumonia caused by MDR pathogens	44	Tracheal aspirates Urine culture Oral/rectal swab	3/week 3/week 1/week	44 (100)	70% (Aspirates) 88% (All cultures)
Papadomichelakis E et al. [6]	Bacteremia caused by gram-negative bacilli	55	Tracheal aspirates Rectal swabs	2/week 1/week	43 (78)	66% (Aspirates) 70% (Rectal swabs) 86% (All cultures)
Blot S et al. [8]	Bacteremia caused by MDR gram-negative bacilli	157	Tracheal aspirates Urine culture Oral/rectal swab	3/week 3/week 1/week	157 (100)	75% (All cultures)
Depuydt P et al. [14]	VAP caused by MDR pathogens	86	Tracheal aspirates Urine culture Oral/rectal swab	3/week 3/week 1/week	86 (100)	69% (Aspirates) 82% (All cultures)
Reddy P et al. [17]	Bacteremia caused by ESBL *Enterobacteriaceae*	102	Rectal swab	1/week	46 (55)	76%
Sreeramoju P et al. [18]	Infections caused by gram-negative bacilli[e]	24	Tracheal aspirates	1/week	24 (100)	46%

VAP ventilator-associated pneumonia, *MDR* multidrug resistant, *BAL* broncho-alveolar lavage, *ARDS* acute respiratory distress syndrome, *ESBL* extended-spectrum beta-lactamase-producing *Enterobacteriaceae*

[a] In episodes in which results from surveillance cultures were available

[b] Tracheal aspirates, BAL, or protectedspecimen brush (PSB)

[c] Tracheal aspirates or PSB

[d] Plugged telescopic catheter

[e] Central line-associated bacteremia, surgical site infection or ventilator-associated pneumonia

rate of empiric appropriate therapy was 85%, which was significantly higher than what would have been achieved by following the American Thoracic Society guidelines or the locally used, strictly empirical scheme.

The data by Papadomichelakis et al. and Jung et al. add to the number of studies showing good concordance between SC and infectious etiology resulting in benefits in terms of appropriateness of empiric therapy [6–11]. However, previous reports have found more variable predictive values, depending upon surveillance methodology and underlying prevalence of MDR infection [5, 12, 13]. A prerequisite for good positive and negative predictive values seems to be a sampling frequency of at least twice weekly. Although the Jung et al. paper used a once-weekly surveillance, a larger previous report using the same approach provided disappointing results (Table 1). In contrast to sampling frequency, the relative contribution of sampling distinct colonization sites is more unclear. Extending SC to more sites increases sensitivity [6, 10, 14], a high negative predictive value of SC (>90% in [15–18]) increases its antibiotic-saving potential, as it reliably defines a patient category in which extensive broad-spectrum antimicrobial coverage is unnecessary. On the other hand, if the number of false positive surveillance results increases, this gain can be rapidly lost. As yet, the optimal trade-off is to be defined. However, surveillance-assisted empiric therapy has been associated with atleast a theoretical reduction in antibiotic consumption, by

comparing it with hypothetical, strictly empirical schemes [10, 11, 14]. Finally, the added value of surveillance-assisted empiric therapy is highly dependent on the local microbial ecology and the patient's risk profile for MDR infection. As more reports solidify the clinical usefulness of SC, cost remains probably the most important factor prohibiting a general use of systematic SC [10, 11]. Obviously, ICUs with a high prevalence of MDR will benefit the most, as will be patient populations with a high risk for MDR infection, such as patients with a complex history, a prolonged hospital stay and numerous previous antibiotics. To reduce the cost one can consider restricting surveillance to this 'difficult' patient category.

Let us return to daily practice: are systematic SC an option to find the balance between high rates of initial appropriate antibiotic therapy on one hand, and a rationed use of broad-spectrum drugs at the other, and does their contribution justify their cost? Four considerations have to be made: (1) what is the local prevalence and pattern of MDR? (2) How appropriate is current empirical therapy and, if suboptimal, can it easily be increased through adaptation of an empirical scheme? (3) What are the resources available for microbiological work-up and what is the willingness to invest? (4) How urgent is the need to restrict the use of broad-spectrum antibiotics? If one would decide to adopt a systematic surveillance program, careful evaluation of appropriateness and consumption of empiric therapy before and after intervention would significantly add to the discussion about the value of surveillance.

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