Chapter 6

Gut Microbiology: Surveillance Samples for the Detection of the Abnormal Carrier State

Introduction

Critical illness impacts all organ systems such as lungs, heart, and gut. The gut also includes the vast living microbial tissue of the indigenous, mainly anaerobic, flora. This enormous bacterial tissue is embedded in the mucous layer and covers the inner wall of the gut. Amongst the aerobic Gram-negative bacilli (AGNB) only the indigenous *Escherichia coli* is carried by healthy people in the gut. Critical illness converts the normal carrier state of *E. coli* into carriage of abnormal AGNB, including *Klebsiella*, *Enterobacter*, *Pseudomonas* species, and methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. It is hypothesized that receptors for AGNB and MRSA are constitutively expressed on the mucosal lining, but are covered by a protective layer of fibronectin in the healthy mucosa. Significantly increased levels of salivary elastase have been shown to precede AGNB carriage in the oropharynx in post-operative patients and the elderly [2, 3]. It is probable that in individuals suffering both acute and chronic underlying illness, activated macrophages release elastase into mucosal secretions, thereby denuding the protective fibronectin layer. It is thought that this possible mechanism is a deleterious consequence of the inflammatory response encountered during and after illness. This shift towards abnormal flora due to underlying disease is aggravated by most iatrogenic interventions in the patient requiring intensive care including mechanical ventilation. Gut protection using H_2 antagonists and antimicrobials are commonly applied in the critically ill. H_2 antagonists increase gastric pH, thereby impairing the gastric acidity barrier [4]. Antimicrobials that are active against the indigenous mainly anaerobic flora, and that are excreted via bile into the gut, may disturb the gut ecology [5]. Integrity of both physiology and flora is essential for the individual's defense against carriage of AGNB. The impairment of these two factors promotes the overgrowth of abnormal potentially pathogenic micro-organisms (PPM), such as AGNB in concentrations of $>10^5$ colony forming units (CFU) per milliliter or gram of feces [6].

Gut overgrowth of abnormal flora is not only a marker of critical illness, but harms the patient as it is a disease in itself. In addition, gut overgrowth of abnormal flora has a major epidemiological impact on the other patients in the intensive care unit (ICU) and on the ICU environment.

Clinical Impact of Gut Overgrowth

Intestinal overgrowth with AGNB causes systemic immuno-paralysis [7]. Together with the depressed immunity, high concentrations of AGNB and MRSA in the throat and gut may result in pneumonia [8] and septicemia [9] following aspiration into the lower airways and translocation in the terminal ileum. Gut overgrowth guarantees amongst the AGNB population the presence of antibiotic-resistant strains producing enzymes that neutralize the antimicrobials [10]. The salivary and fecal concentrations of the parenterally administered antimicrobials are in general not bactericidal for the PPM present in high numbers in the gut, and create an environment in which antibiotic-resistant strains readily survive.

Epidemiological Impact of Gut Overgrowth

The higher the salivary and fecal concentrations of AGNB and MRSA, the higher the possibility of PPM transmission via the hands of carers [11–13]. Acquisition of PPM invariably leads to carriage, as the critically ill are unable to clear the acquired AGNB and MRSA. Carriers of abnormal bacteria in overgrowth shed these micro-organisms into the environment and determine the contamination level of the inanimate environment, including beds, tables, telephones, and floors [14].

Definitions

Surveillance Samples

Surveillance samples are defined as samples obtained from body sites where PPM may potentially be carried, i.e., the digestive tract comprising the oropharyngeal and rectal cavities [15]. Surveillance cultures should be distinguished from surface and diagnostic samples.

Surface Samples

Surface samples are taken from the skin, such as axilla, groin, and umbilicus, and from the nose, eye, and ear. They do not belong to a surveillance sampling protocol because positive surface swabs merely reflect the oropharyngeal and rectal carrier states.

Diagnostic Samples

Diagnostic samples are from internal organs that are normally sterile, such as lower airways, blood, bladder, and skin lesions. They are only taken on clinical indication. The endpoint of diagnostic samples is clinical, as they aim to prove microbiologically a clinical diagnosis of inflammation, both generalized and/or local.

Endpoints

The aim of obtaining surveillance cultures is the determination of the microbiological endpoint of the carrier state of PPM [16]. Carriage or a carrier state exists when the same bacterial strain is isolated from at least two consecutive surveillance samples of the ICU patient in any concentration over a period of at least 1 week. Carriage implies persistence of a PPM, and is distinguished from acquisition or transient presence. Surveillance samples are not useful for diagnosing infection of lungs, blood, bladder, or wounds. Diagnostic samples are required for this purpose.

Sampling for Surveillance purposes

Which Patients?

Only the most critically ill patients require intensive microbiological monitoring using surveillance samples for the detection of the abnormal carrier state of AGNB and MRSA. Due to the severity of their illness they require intensive care, including mechanical ventilation, for a minimum of 3 days. In general they have impaired gut motility and, hence, are at high risk of developing throat and gut overgrowth.

What Samples?

A surveillance program for this type of patient includes samples from both the oropharynx and gut. Potential pathogens carried in the throat and gut cause

pneumonia [8] and septicemia [9], respectively. These two serious infections are responsible for a high rate of mortality. Potential pathogens present in overgrowth in the throat and gut are implicated in transmission via the hands of carers, in particular in outbreak situations. A throat and rectal swab are taken to detect the oropharyngeal and gut carriage of AGNB and MRSA. Rectal swabs must be coated with stool. As MRSA has an affinity for the skin, skin is sampled only if lesions are present.

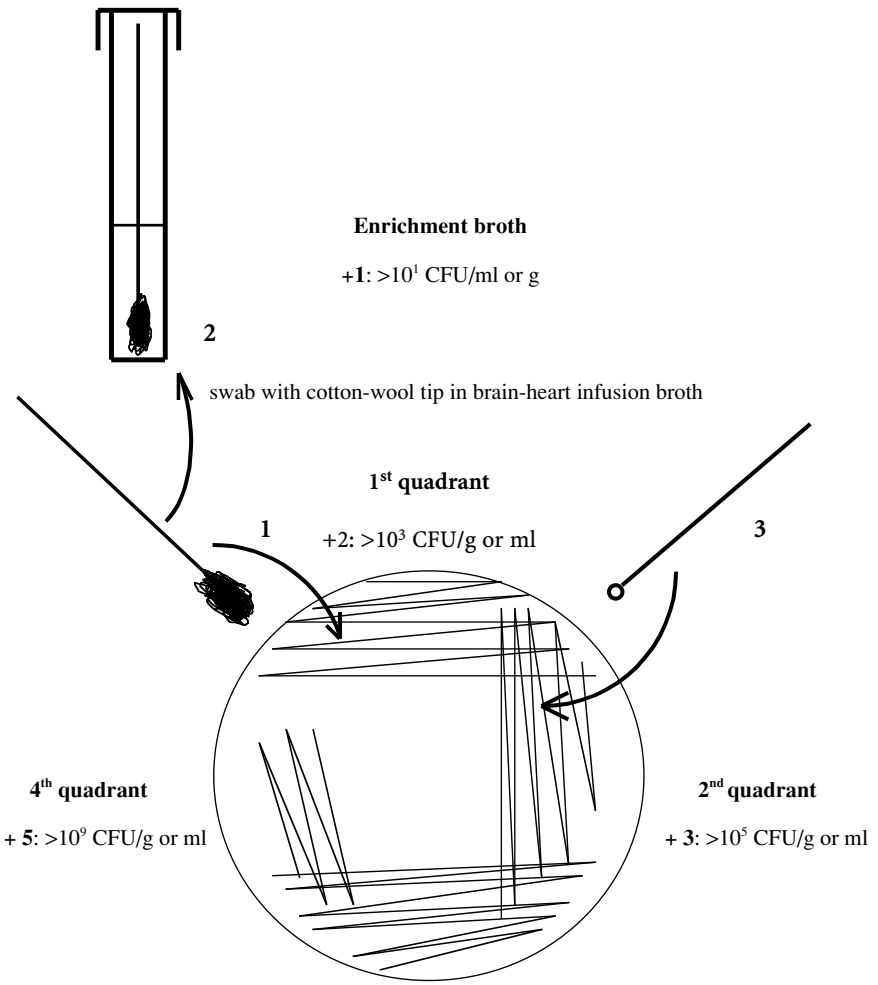
When?

Surveillance sets are obtained on admission and thereafter twice weekly (e.g., Monday, Thursday) throughout the ICU stay, in order to distinguish carriage due to PPM imported in the admission flora ("import") from carriage due to ICU-associated PPM acquired in the oropharynx and gut during the ICU stay ("nosocomial", "secondary" or "super" carriage).

Microbiological Procedures

Throat and rectal swabs are processed qualitatively and semi-quantitatively, including an enrichment broth, to detect the level of carriage of the three types of target micro-organisms, AGNB, *S. aureus* sensitive and resistant to methicillin, and yeasts [1, 17].

Three solid media, MacConkey (AGNB), staphylococcal, and yeast agar, are inoculated using the four-quadrant method, and a brain-heart infusion broth culture to detect low-grade carriage is included (Fig. 1). Each swab is streaked onto the three solid media, then the tip is broken off into 5 ml of enrichment broth. All cultures are incubated aerobically at 37°C. The MacConkey plate is examined after 1 night, the plates for staphylococci and yeasts after 2 nights. In addition, if the enrichment broth is turbid after 1 night's incubation, it is then inoculated onto the three media. A semi-quantitative estimation is made by grading growth density on a scale of 1+ to 5+, as follows (Table 1): growth in broth only=1+ (approximately 10 micro-organisms/ml), growth in the first quadrant of the solid plate=2+ ($>10^3$ CFU/ml), in the second quadrant=3+ ($>10^5$ CFU/ml), in the third quadrant=4+ ($>10^7$ CFU/ml), and on the whole plate=5+ ($>10^9$ CFU/ml). Macroscopically distinct colonies are isolated in pure culture. Standard methods for identification, typing, and sensitivity patterns are used for all micro-organisms. All data are entered into the computer. A simple program enables the intensive care specialist to view the microbiological overview chart of each long-stay patient at the bedside. Tables 2 and 3 show typical examples.



1. inoculation of solid medium (1st quadrant)

2. cotton-wool tip in liquid medium to detect low concentrations

3. diluting using different loops

Fig. 1. Processing surveillance swabs using the four-quandrant method and enrichment step

Table 1. Comparison of the surveillance (throat/rectal) swabs and (salivary/fecal) specimens for the detection of the level (growth density) of carriage of aerobic Gram-negative bacilli, *Staphylococcus aureus*, both sensitive and resistant to methicillin, and yeasts

Four-quadrant method with enrichment step	Growth density	Dilution series
Semi-quantitative swab method		Quantitative specimen method
1+	Very low	10^1
2+	Low	10^3
3+	Moderate	10^5
4+	High	10^7
5+	Very high	10^9

Moderate growth density, i.e., >3 or $>10^5$ colony forming units, reflects overgrowth

Table 2. Oropharyngeal and gastrointestinal carriage detected by surveillance samples is shown in combination with the colonization/infection data obtained from the diagnostic samples of lower airways, bladder, and blood. The overview chart shows that both primary and secondary endogenous infections occur after 48 h

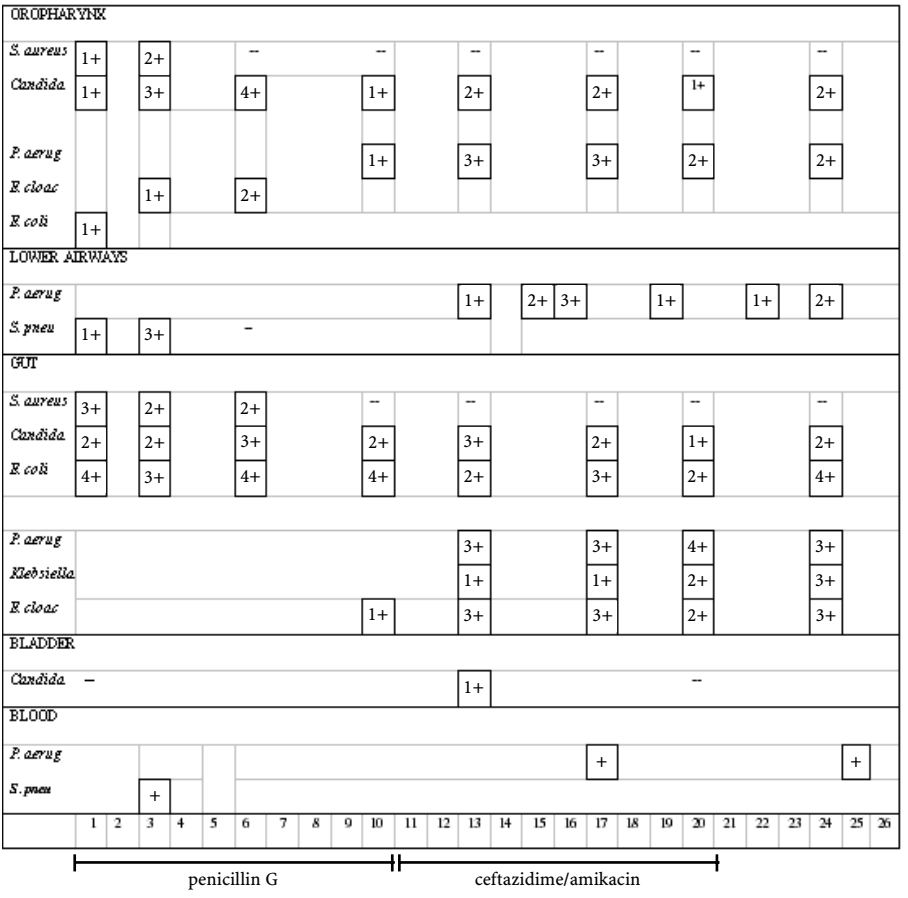
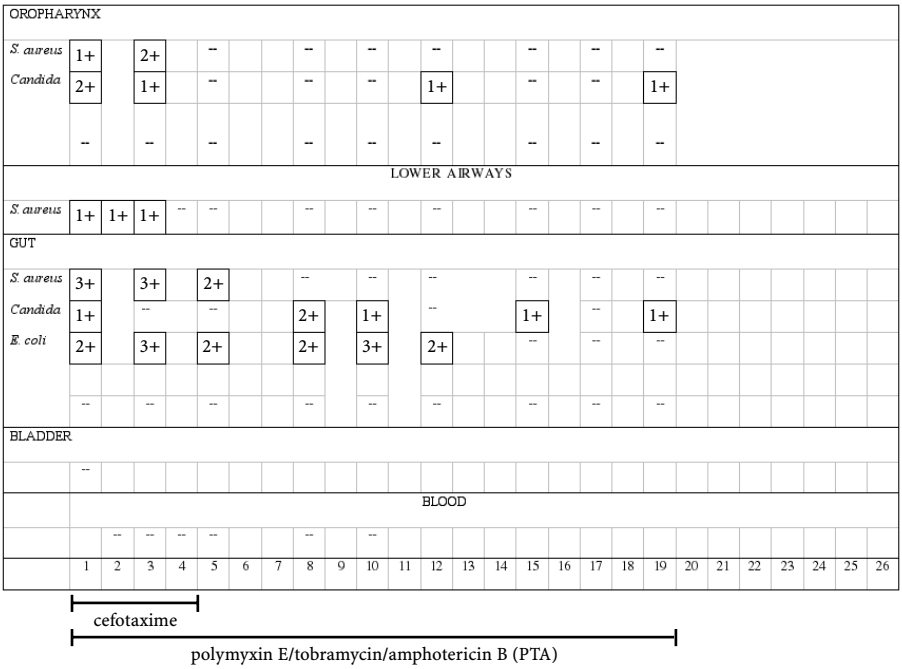


Table 3. This microbiological chart shows the pattern of a trauma patient who received the full protocol of selective decontamintion of the digestive tract, immediately on admission. Cefotaxime controlled primary endogenous infection developing within the 1st week, and the enteral polymyxin E/tobramycin/amphotericin B (PTA) prevented the development of supercarriage and subsequent supercolonization and infection



Interpretation of Surveillance Samples

Surveillance cultures allow the intensive care specialist to distinguish the normal from the abnormal carrier state, overgrowth from low-level carriage, and endogenous from exogenous infections in combination with diagnostic samples.

Normal versus Abnormal Carriage

Surveillance swabs processed for one group of target micro-organsims, AGNB, using an inexpensive MacConkey agar plate yield a positive or negative result after 18 h of incubation. AGNB, including *E. coli,* are uncommon in the oropharynx, whilst healthy people carry their own indigenous *E. coli* in the intestine in concentrations varying between 10^3 and 10^6 CFU/ml or g of feces [16] (Table 4). There are no other AGNB, including *Klebsiella*, *Proteus*, *Morganella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Acinetobacter*, and

Table 4. Surveillance cultures: normal and abnormal values (*CFU* colony forming units, *AGNB* aerobic Gram-negative bacilli, *MRSA* methicillin-resistant *Staphylococcus aureus*)

	Normal Values	Abnormal Values
1. Throat	*S. aureus*/*C. albicans* (30% carriage)	*S. aureus*/*C. albicans* (30% carriage)
- Swab	< 3+ CFU/ml	>3+ CFU/ml
- Saliva	$< 10^5$ CFU/ml	$>10^5$ CFU/ml
		E. coli, AGNB, MRSA in any concentration
2. Rectum	Indigenous *E. coli* (100% carriage)	Indigenous *E. coli* (100% carriage)
	S. aureus/*C. albicans* (30% carriage)	*S. aureus*/*C. albicans* (30% carriage)
- Swab	<3+ CFU/g	>3+ CFU/g
- Feces	$< 10^5$ CFU/g	$>10^5$ CFU/g
		AGNB/MRSA in any concentration
3. Vagina	See rectum	See rectum

Pseudomonas species, in either the throat or gut. Interpreting the staphylococcal plate requires 2 nights of incubation. About one-third of the healthy population carries methicillin-sensitive *S. aureus*. The isolation of MRSA is always abnormal [1]. Yeasts also require 48 h of incubation, and can be carried by approximately 30% of the healthy adult population in concentrations of <3+ or $<10^5$ CFU/ml of saliva and per gram of feces. However, yeast overgrowth promotes translocation and fungemia.

Low-Grade Carriage versus Overgrowth

Oropharyngeal and intestinal overgrowth is defined as >3+ or $>10^5$ micro-organisms per ml of saliva and/or g of feces and is distinguished from low-grade carriage of <3+ or $<10^5$ micro-organisms [1, 6, 17]. Individuals with a chronic disease, such as chronic obstructive pulmonary disease, generally carry

Table 5. Strengths and weaknesses of both surveillance methods of infection only and of infection combined with carriage

Strengths	Weaknesses
Surveillance of infection (solely diagnostic samples)	Surveillance of infection (solely diagnostic samples)
• Already routine • Easy to fulfil • Number of infections per 1,000 device-days: useful to know the trends in infection rates in one unit	• Substantial delay between the detection of a problem and the implementation of the appropriate measures to control it, because of the extra work required to identify the pathogenesis of the problem • Cost-effectiveness: has to be tested • Time cut-off of 48 h: not accurate for the estimation of infection due to ICU micro-organisms • Value of method for interhospital comparison: limited • Detection of resistance, transmission and outbreaks: late
Surveillance of infection/carriage (diagnostic samples combined with surveillance samples)	Surveillance of infection/carriage (diagnostic samples combined with surveillance samples)
• More accurate estimation of infections due to ICU-acquired micro-organisms • Early implementation of the appropriate preventive measures according to the pathogenesis of the infections • Detection of resistance at an early stage • Detection of transmission at an early stage • Indispensable in control of an outbreak • Monitoring the efficacy of selective digestive decontamination	• Workload for laboratory is higher • Cost-effectiveness: has to be tested • Value of method for interhospital comparison: has to be tested • Surveillance cultures: unpopular amongst traditional microbiologists

abnormal flora in low concentrations once the forced expiratory volume in 1 s is <50% [18]. The low-level carrier status is mainly due to the presence of clearing mechanisms such as swallowing, chewing, and peristalsis. However, patients who require mechanical ventilation for a minimum of 3 days generally have impaired gut motility and readily develop overgrowth [19]. Gut overgrowth is an independent risk factor for (1) colonization/infection of internal organs [8, 9], (2) the expression of an antibiotic-resistant mutant among the microbial population [10], and (3) transmission of (often antibiotic-resistant) micro-organisms [11–13].

'Imported' versus 'Nosocomial' Carriage

Knowledge of the carrier state, at the time of admission and subsequently, is crucial to the management of infection on the ICU. Hygiene measures will only have an impact on infections due to externally transmitted micro-organisms. A primary endogenous infection caused by a PPM imported by the patient into the ICU in the admission flora can only be managed effectively with knowledge of the carrier state. It is obvious that hand hygiene fails to eradicate carriage in the throat and gut detected by surveillance samples on admission. However, that information enables the intensivist to implement isolation and to reinforce hygiene measures as soon as possible following admission. Two recent studies show that MRSA and ceftazidime-resistant AGNB were identified in 23.8% and 52.1% of patients within the first 72 h of admission to the ICU [20, 21].

Interaction between Carriage and Infection

With the structured approach, which combines data from surveillance and diagnostic samples (Tables 2 and 3), infection can be categorized into three different groups [22].

1. Primary endogenous infections are the most frequent; the incidence is ca 15% and varies between 60% and 85%, depending on the severity of illness of the patient population studied [23–26]. They are caused by both "community" and "hospital" micro-organisms carried in the throat and gut on admission. These episodes typically occur within the 1st week of the ICU stay. Examples include lower airway infection in a previously healthy individual caused by *Streptococcus pneumoniae*, or "hospital"-type organisms such as *Klebsiella pneumoniae* in patients with underlying disease. The incidence of primary endogenous infection is reduced by adequate parenteral antibiotics, e.g., cefotaxime, given immediately on admission, for 4 days [27–29].
2. Secondary endogenous infections are caused by ICU-associated micro-organisms appearing late in the ICU stay, in general after 1 week [23]. These ICU micro-organisms are acquired first in the oropharynx, followed by the stomach and gut. One-third of ICU infections are secondary endogenous infections [23–26]. Significantly, in patients not taking antibiotics on admission, almost all such infections develop only in patients who have previously had a primary endogenous infection, i.e., a subset of critically ill patients who develop more than one infection during their ICU stay [25]. Only the topical application of non-absorbable antimicrobials polymyxin E/tobramycin/amphotericin B (PTA) throughout the ICU stay has been shown to control secondary endogenous infection [11–13].
3. Exogenous infections are less common (approximately 15%) [23–26], but may occur throughout the patient's ICU stay and are caused by "hospital" bacteria, in particular *Acinetobacter* spp., *Pseudomonas* spp., and MRSA

without previous carriage. Typical examples are lower airway infections caused by *Acinetobacter* spp. in patients with a tracheostomy whether they receive PTA or not [30, 31]. A high level of hygiene is required to control exogenous infections [32].

To control the three types of infection that may occur on the ICU, the enteral PTA antimicrobials are added to the parenteral cefotaxime, whilst a high level of hygiene is maintained at all times. Surveillance samples of throat and rectum are an integral part of this infection control program for the ICU patient, for the following reasons: (1) to monitor the compliance and efficacy of PTA, (2) to detect any exogenous problems on the ICU, and (3) to detect the emergence of resistant micro-organisms at an early stage. The full four-component strategy is termed selective decontamination of the digestive tract (SDD) [33–35].

Role of Surveillance Samples in Infection Control in the ICU Patient

Recent studies using surveillance cultures of throat and rectum to detect the carrier state demonstrate that only infections occurring after 1 week of ICU stay are due to microbes transmitted via the hands of health care workers [23–26]. The incidence varies between 15% and 40%, depending on the severity of the illness. Micro-organisms related to the ICU environment are first acquired in the oropharynx. In the critically ill, oropharyngeal acquisition invariably leads to secondary or super-carriage. The subsequent build up to digestive tract overgrowth, which can then result in colonization of normally sterile internal organs, takes a few days. Finally, it is the degree of immunosuppression of the ICU patients that determines the day of colonization leading to an established secondary endogenous or super-infection. The other type of ICU infection is the exogenous infection [30–32] due to breaches of hygiene. The causative bacteria are also acquired on the unit but are never present in the throat and/or gut flora of patients. For example, long-stay patients, particularly those who receive a tracheostomy on respiratory units, are at high risk of exogenous lower airway infections. Purulent lower airway secretions yield a micro-organism that has never been previously carried by the patients in the digestive tract flora, or indeed in their oropharynx. Although both the tracheostomy and the oropharynx are equally accessible for bacterial entry, the tracheotomy tends to be the entry site for bacteria that colonize/infect the lower airways. However, the major infection problem is primary endogenous and the micro-organisms involved do not bear any relation to the ecology of the ICU. A recent study compared the traditional 48-h cut-off and the criterion of the carrier state to find that the time cut-off significantly over-estimated the magnitude of the nosoco-

mial problem [26]. This approach to the carrier state may be more useful for interhospital comparison, as only infections due to micro-organisms acquired on the different units are compared, independent of the severity of illness.

In identifying the right population with primary endogenous infections, the classification using the carrier state avoids blaming staff for all infections occurring after 48 h for which they are not responsible. Knowledge of the carrier status thus prevents fruitless investigation of apparent cross-infection episodes. Secondly, without surveillance samples, exogenous infections are impossible to recognize, at least at an early stage when only diagnostic samples such as tracheal aspirate, urine, and blood have been tested. Finally, knowledge of the carrier state using surveillance cultures on admission and twice weekly is an effective strategy for early identification of carriers of multi-resistant micro-organisms, including AGNB such as *Acinetobacter baumannii* [36], MRSA [21, 23, 25, 37], and vancomycin-resistant enterococci [38], both on admission and during the ICU stay. Surveillance cultures, in particular of the oropharynx, that become positive for a PPM during the ICU stay reveal ongoing transmission and an impending outbreak long before the diagnostic samples yield the outbreak strain [39]. This surveillance strategy optimizes targeted infection control interventions, including (1) hand hygiene, (2) isolation, (3) personal protective equipment, and (4) the care of the patient's equipment to control transmission from one patient-carrier to another via hands of the carers.

Future Lines of Research on Surveillance Samples in the ICU Patient

Most infection surveillance programs include all patients admitted to the ICU whether they stay a few days or 2 weeks [40, 41]. The inclusion of a large number of relatively short-stay patients with a low risk of infection tends to dilute the total rates of infection by increasing the size of the denominator. However, low percentages look good to the manager of the hospital, but do not allow room for improvement, i.e., the detection of a significant reduction in infection rate following the introduction of an intervention [24]. We believe that critically ill patients benefit from a surveillance program of both infection and of carriage [42, 43], in particular in combination with SDD [33–35].

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SECTION TWO
Antimicrobials