Conseil Supérieur d'Hygiène

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GUIDELINES FOR THE CONTROL AND PREVENTION OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* TRANSMISSION IN BELGIAN HOSPITALS

Groupement pour le Dépistage, l'Etude et la Prévention des Infections Hospitalières -
Groep ter Opsporing, Studie en Preventie van de Infecties in de Ziekenhuizen
(GDEPIH - GOSPIZ)

1 Introduction

Staphylococcus aureus is a leading cause of skin and soft tissue infections, infections of surgical sites and catheter sites, of pneumonia, bacteraemia and osteo-articular infections. Over the past two decades, the incidence of methicillin-resistant *S. aureus* (MRSA) as an agent of nosocomial infection has increased in many parts of the world. Recent molecular epidemiological studies have established that methicillin-resistance is acquired by *S. aureus* through the integration of a large genomic resistance island called staphylococcal cassette chromosome mec (SCCmec)[1]. The analysis of large collections of MRSA strains of worldwide origin indicates that these genetic transfers have occurred only a limited number of times. The worldwide expansion of MRSA has resulted from dissemination of about a dozen epidemic clones[2]. Thus, nearly all cases of MRSA colonisation and infection result from exogenous transmission from other MRSA carriers in healthcare institutions. This underlines the crucial importance of interrupting nosocomial transmission to control MRSA infection. In addition, community-acquired MRSA infections have recently been reported in the USA, Australia and France, apparently caused by novel clones of hyper-virulent methicillin-susceptible *S. aureus* strains that have recently acquired the *SCCmec* gene.

Epidemic MRSA strains have been shown to cause outbreaks of cross-infection in hospitals. They disseminate between healthcare facilities over large geographic areas through colonised and/or infected patients[3]. They cause a net increase in the rate of nosocomial infections[4], significant and increased morbidity[5,6], mortality[6,7] and cost[8,9], are more difficult to treat and respond less well to therapy. Recent estimates of the cost attributable to MRSA infection in hospitalised patients ranged from 10 000 to 36 000 Euros[8]. A meta-analysis of studies indicates that the mortality of MRSA bacteraemia is significantly increased as compared to MSSA bacteraemia (Pooled odds ratio: 1.93)[7].

In Europe, the prevalence of methicillin-resistance among *S. aureus* varies dramatically between countries (EARSS)[10]. It ranges from > 30% (and is still rising) in countries like the UK, France, Italy, Spain and Portugal, to less than 2% in the Netherlands and Scandinavia, where a rigid national policy is in place. The latter is based upon putting patients transferred from other countries in quarantine, on surveillance, barrier precautions, carrier decontamination and cohort nursing. Although they often fail to be properly evaluated, these control strategies seem to decrease MRSA transmission both in epidemic and endemic settings. The risk of transmission from a non-isolated patient is 16 to 38 times[11,12] higher than from isolated patients. Six cost-benefit studies have concluded that these control policies are cost effective in situations where carriage rates on admission vary between 0.5 to 20 %, efficacy of control measures between 14 and 80 % and rate of infection among colonised patients is between 20 and 60 %[13,14,15,16]. The world-wide development in 2002 (which was also noted in Belgium[17]) of MRSA strains intermediately resistant to vancomycin (VISA)[18] and the emergence in the USA[19] of *S. aureus* fully resistant to vancomycin following the acquisition of the enteroccocal *vanA* gene have further narrowed down the therapeutic options. Therefore, the cost-benefit of vigorous MRSA control policies has been grossly underestimated.

A Belgian multicentre survey has shown that the proportion of MRSA among patients with *S. aureus* bacteraemia in acute care hospitals had risen from 10% in 1984 to 30% in 1992[20]. In 1993-94, national guidelines for the control of MRSA in hospitals were developed and published by the *Groupement pour l'Etude, le Dépistage et la Prévention des Infections Hospitalières* (GDEPIH-GOSPIZ)[21]. A national MRSA surveillance program was launched in collaboration with the federal Scientific Institute of Public Health and the reference laboratory for staphylococci (ULB-Erasme) to monitor the prevalence and incidence of MRSA in Belgian hospitals[22] and a decrease was observed after more than 80 % of the hospitals had adopted the national guidelines. The proportion of MRSA among bloodstream isolates decreased to a mean 23 % in 1999; the proportion of MRSA among clinical *S. aureus* isolates dropped from 24 to 14 % between 1994 and 1998 whereas the incidence of nosocomial acquisition declined steadily from a mean of 3.7 to 2.0 cases per 1000 admissions (National Surveillance of MRSA Report, B. Jans et al). However, this encouraging trend has reversed since 1999: in 2002, the MRSA ratio increased once again to 24 % and the incidence reached 3 per 1000. Molecular epidemiological surveillance showed a dramatic shift in the epidemiological distribution of epidemic MRSA strains in Belgium: a gentamicin susceptible clone B[23] and more recently four other epidemic clones including the UK EMRSA-15 and 16 gradually replaced the multi-resistant, pan-European MRSA clone A that caused most outbreaks in the 1980s.

This recent resurgence of MRSA and frequent outbreaks in Belgian hospitals has raised serious concern among health professionals and authorities. This recrudescence can be caused by different factors: new, possibly more transmissible MRSA clones, selective pressure by increasing antibiotic

consumption, establishment of a large MRSA reservoir among chronically colonised patients in acute and chronic care facilities[24,25], increased turnover and transfer of patients within and between care facilities and decreased surveillance delaying implementation of additional barrier precautions. Last but not least, it might be that shortage of skilled nursing personnel and increasing work pressure has decreased the compliance with standard precautions and additional barrier precautions.

2 Development of the 2003 revision of the guideline

In June 2002, concerned with the recrudescence of MRSA in Belgium, the GDEPIH-GOSPIZ and the Health Council proposed to revise the national guidelines and update the recommended policies with evidence from studies published in the last decade and dealing with the local epidemiological situation.

A guideline revision group composed of B. Gordts, Y. Glupczynski, P. De Mol, C. Suetens, B. Byl, B. Jans, F. De Meerleer and M. Struelens reviewed the 1993 version of the guidelines based upon personal literature and the annotated bibliography from guideline development groups in the Netherlands, UK and USA. The group also examined national MRSA surveillance reports and unpublished recent surveys from Belgian hospitals and nursing homes, published a draft proposal on the GDEPIH/GOSPIZ web page in April 2003 and discussed this proposal during a national GOSPIZ-GDEPIH symposium on April 29 2003. In July 2003, the MRSA working group of the Health Council and the GOSPIZ-GDEPIH bureau issued the final version of the guidelines.

The document recommends how the MRSA problem should be managed in Belgian hospitals in 2003. Some of the recommendations go beyond the present practice in some hospitals. However it must be emphasised that a shortage of resources cannot justify disregarding the recommendations. Hospital administrators should provide the necessary resources and encourage the hospital hygienists and hospital hygiene committee to implement the recommendations. Moreover, the hospital administrators must correctly inform hospital staff about MRSA management and obtain the necessary commitment for the correct implementation of these measures.

3 Identification of MRSA and susceptibility testing for oxacillin-resistance

MRSA management starts with adequate microbiological techniques. The *in vitro* identification of MRSA comprises three features: the identification of *S. aureus*, the determination of oxacillin-resistance (detection and confirmation), and the antimicrobial susceptibility testing (AST) for other antimicrobial agents.

3.1 Identification of *S. aureus*

Identification of the genus *Staphylococcus*: staphylococci are gram-positive cocci that mostly grow as irregular grape-like clusters. *In vitro* they behave as non-motile, non- sporeforming catalase positive facultative anaerobes. Staphylococci grow on agar containing 6.5% NaCl and on blood agar within 18 to 24 hours as white to yellow, smooth, circular often haemolytic and raised colonies of 1 - 3 mm in diameter of butyrous consistency. Haemolysis of the medium by MRSA strains can occur slowly and be hard to notice.

Identification of *S. aureus*: Standard identification of *S. aureus* can be done by detecting the clotting activity on plasma due to the production of coagulase. The tube test for free coagulase is definitive, whereas the coagulase slide test serves as a rapid screening technique.

Rapid presumptive identification can be performed with one of the latest-generation latex agglutination tests which combine the detection of clumping factor and protein A with antibodies against *S. aureus* specific capsular polysaccharides or group-specific cell surface antigens[26] (Staphaurex Plus / Murex Diagnostics; Pastorex Staph Plus / Sanofi Diagnostics Pasteur; Staphytect Plus / Oxoid; Slidex Staph-Plus / bioMérieux). In some series, these tests are reliable as a screening for *S. aureus* (accuracy >98 %), but because of inter-lot variability of these tests (false positive and false negative results, specificity 73 to 82 % in some series), it might be preferred to confirm the identification of *staphylococcus aureus* with tube coagulase at least for the first isolate for each patient.

3.2 Susceptibility testing for oxacillin-resistance

Oxacillin-resistance in *S. aureus* is determined by the *mecA* gene, which encodes for the expression of an additional penicillin-binding protein, PBP2a, which binds β-lactam antibiotics with a lower affinity than PBP2, the major target for the antibiotic. Many other factors besides the *mecA* gene are involved in the expression of oxacillin-resistance, explaining the existence of homogeneous and heterogeneous MRSA populations. Some strains only express resistance when exposed to antibiotics. Thus, although the detection of oxacillin-resistance is straightforward for most MRSA isolates, the detection of low-level or heterogeneously resistant strains can be very difficult.

3.2.1 Detection of oxacillin- resistance

Not all dilution methods (agar, broth or automated methods) adequately detect oxacillin-resistance in all circumstances[27].

The routine detection of oxacillin-resistance can be performed with agar diffusion (oxa-1 disc) or oxa-screen agar. All phenotypic assays must be carefully calibrated (medium, inoculum, temperature and duration of incubation) and quality controlled. False negative results are occasionally seen when the test is not performed strictly according to the NCCLS guidelines[27,28]. It is imperative that a direct colony suspension with a 0,5 McFarland turbidity standard be inoculated on Mueller-Hinton agar, incubated in ambient air at ±35°C for a full 24 hours.

Recent reports indicate that the cefoxitin disc diffusion method may be more sensitive and specific than these standard methods to detect low-level resistance to oxacillin of heterogeneous MRSA strains by inducing the expression of the *mecA* gene[29]. An inhibition zone with a diameter smaller than 20 mm due to a 30 µg cefoxitin disc is indicative of MRSA. Whilst confirmation of these results by larger studies of Belgian MRSA isolates is awaited, a practical option is to add a cefoxitin disc to the standard disc diffusion plate.

Many of the early generation automated AST methods have been reported to be unreliable as a means of detecting MRSA. More recent versions have demonstrated adequate performance (sensitivity > 97%), including the Vitek II system (bioMérieux) and Micro Scan Rapid (Dade Behring). Evaluation of the Phoenix system (Becton-Dickinson) is ongoing. It remains to be confirmed how well these methods perform on heterogeneous MRSA populations with a low level of resistance.

For any *S. aureus* isolate that appears susceptible to oxacillin according to the standard procedures but resistant to at least one of the 4-fluoroquinolones, aminoglycosides or tetracyclines, oxacillin-susceptibility must be confirmed.

3.2.2 Confirmation of oxacillin-resistance

Oxacillin-resistance must be confirmed with another method than the screening method at least once per patient and in case of any atypical results or discrepancy between the methods mentioned above.

The golden standard for confirming oxacillin-resistance is demonstrating the presence of the *mecA* gene by means of PCR. The test is performed in all Belgian Centres for Molecular Diagnostics. Other techniques that demonstrate *mecA* might become available in Belgium in the future (Evigene / Staten Serum Institute; Velogene rapid MRSA identification assay / ID Biomedical Corp.)

The presence of PBP2a can also be demonstrated by means of a latex agglutination test (Denka Senken, Oxoid) with a specificity of 100% and a sensitivity of > 97%[30]. This rapid test offers a speedy alternative for confirming oxacillin-resistance.

When the confirmation tests mentioned above are unavailable, the oxa-screen test (Mueller-Hinton II medium supplemented with 4% NaCl and 6 mg/L oxacillin) can be used. However, it must be emphasized that degenerate variants (small colony variants) of MRSA may not grow on oxa-screen agar, thus resulting in a false negative interpretation.

3.3 Testing of other antibiotics for MRSA

All MRSA isolates should be reported as resistant to all ß-lactam antibiotics, including ß-lactam/ ß-lactamase inhibitor combinations, cephalosporins and carbapenems. Resistance to ß-lactams may be inferred from testing only oxacillin. It is not advised to test other penicillins, ß -lactam inhibitor combinations, cephems or carbapenems *in vitro*[27] because these antibiotics may appear active *in vitro* on MRSA and can dangerously mislead the clinician.

Mupirocin as well as vancomycin and/or teicoplanin should be tested. Testing gentamicin, rifampin, fusidic acid and linezolid susceptibility is recommended for cases of clinical infection, not for colonisation.

3.3.1 Determination of susceptibility to mupirocin

There are two modes of resistance to mupirocin, viz. high-level (MIC $\geq$ 512 mg/L) and low-level (MIC 8 - 256 mg/L) resistance. The clinical significance of low-level mupirocin resistance is dubious given that the concentration of mupirocin in the 2% ointment exceeds 20,000 mg/L. However, an increased risk of clinical failure with nasal treatment of multi-site MRSA colonisation has been associated with low-level resistance in one study[31]. The risk of mupirocin treatment failure due to high-level resistance on the other hand is well recognized. The rate of high-level resistance has increased to approximately 3 % of MRSA strains in Belgium. Some strains have caused local epidemics.

Mupirocin susceptibility can adequately be tested with the Kirby Bauer disc diffusion method using a paper disc/tablet containing 5 or 10 µg of mupirocin (Oxoid/Rosco) to detect low-level resistance, and / or a 200 µg disc (Oxoid) for high-level resistance. The MIC can be determined by using the E-test (AB Biodisc) or dilution test. Confirmation of high-level resistance can be done at the Staphylococci reference laboratory by PCR for the *mupA* gene.

3.3.2 Determination of susceptibility to vancomycin

Homogeneous glycopeptide intermediate resistant strains (vancomycin MIC of 8 mg/L or teicoplanin 16 mg/L) have been related to clinical failure of glycopeptide treatment. These strains are rare and emerge from MRSA strains in patients treated with a glycopeptide for longer periods of time. They are called GISA, VISA or TISA depending upon the drugs to which they present resistance[32]. Determining staphylococcal susceptibility to glycopeptides (vancomycin and teicoplanin) by means of the disc diffusion methods or first generation automated dilution methods is unreliable.

Screening for GISA should be performed by means of the agar screen technique on clinical isolates of MRSA, at least when dealing with patients failing to respond to glycopeptide treatment[33,34]. A pure culture must be inoculated on a Brain Heart Infusion Agar containing 6 mg/L of vancomycin and inspected for growth after a full 24 hours of incubation. Confirmation of resistance must be performed

by means of population analysis profile and/or electron microscopy (thickened cell wall) at the staphylococci reference laboratory (Erasme-ULB; Pr. M. Struelens).

The clinical significance of heterogeneous glycopeptide intermediate *S. aureus* (hGISA; borderline susceptible strains) is unclear, although recent data suggest that the response to the glycopeptide therapy administered to patients infected by such variants can be poor. Moreover, hGISA can easily select GISA variants in patients being given a prolonged glycopeptide therapy. These strains rarely appear in Belgium[35]. Screening for hGISA can be done by using low concentration screening plates or preferably the E-test "macro-method"[36] (higher inoculum of 2 McFarland incubated on a richer medium like Brain Heart Infusion agar and inspected after 48 hours of incubation; breakpoint for vancomycin or teicoplanin $\geq$ 8 mg/L). Confirmation requires a population analysis profile.

4 Epidemiological investigation and follow-up of MRSA in the institution

Before the local policy for MRSA control can be decided on, it is essential to assess and regularly re-assess the epidemiology of these infections. From one hospital to the other and within the same institution from one period to the other, the incidence of nosocomial acquisition of MRSA and its clinical consequences can vary widely.

In order to assess the importance of MRSA, every healthcare facility should set up a continuous surveillance of MRSA based upon data from their microbiology laboratory, which can be completed by a continuous or periodical participation to the national surveillance of MRSA.

We distinguish two levels of activities in the surveillance of MRSA:

- A system for timely follow-up and rapid feedback of MRSA incidence
- More in-depth follow-up of MRSA indicators and characteristics

4.1 Real time surveillance and rapid feedback (based on ET, Curran et al.[37])

The hospital surveillance must allow for a timely response to an increase in the incidence of MRSA cases in the different wards. This process includes data collection, monthly analysis of the results and discussion of the results and measures to be implemented with the wards involved.

The **data collection** must make it possible to report on a monthly basis the number of new patients colonised and/or infected by MRSA for each ward/unit. For each new MRSA case, the following data (variables) must be collected:

a. Unique patient identifier

b. Date of admission to the hospital

c. Ward/unit where the patient was admitted when MRSA was identified

d. Date of admission to this ward/unit

e. Date of MRSA isolation (sampling date)

f. Acquired during current admission Yes/No
   Exclusion criteria:
   - Positive screening culture on admission
   - Known colonisation or infection from a previous admission or hospital or facility. If no other data are available, an arbitrary cut-off point of 48 hours is used, i.e. nosocomial acquisition is defined as a MRSA strain firstly isolated from a patient who had been hospitalised for more than 48 hours.

g. Ward/unit where the patient acquired MRSA (if different from c)

In order to allow for regular and timely reporting, these data can be entered in a computer (as much as possible with automatic download of existing data). Data entering can be done e.g. in the laboratory computer system or in a database specially developed for this purpose (e.g. NSIHwin module with data import capacity and automatic feedback production by ward).

The feedback will consist in a monthly reporting of the number of new patients colonised or infected by MRSA by unit, ward and as a total for the hospital. It can be presented in different ways:

- List and total number of new cases for that month
- Graphical representation of the evolution of the number of new cases per month:
    - Simple chart: histogram or line chart of the number of cases per month
    - SPC (statistical process control) chart[37,38,39] line chart of the number of new cases per month along with 5 horizontal "reference" lines:
        - Central line: mean (expected value)
        - Warning limit: + 2 standard deviations
        - "Out-of-control" limit: + 3 standard deviations

        - Mean -2 SD and -3 SD
    - Line chart indicating current monthly incidence rate in the unit and the mean for the whole hospital or similar types of ward (e.g., surgery, ICU…). The incidence rate in the unit in the previous year.
- Other methods, e.g. see Quesenberry[40]

This feedback will be produced on a monthly basis and distributed to the heads of the ward and the head physician. A discussion of the results with the ward/unit staff concerned should then identify the possible causes of any increase or stimulate the staff (e.g. incentives) to continue their infection prevention efforts in the case of a stable low rate or a decrease.

4.2 In-depth MRSA surveillance

A more thorough epidemiological analysis of the MRSA problem must allow for a better interpretation of the surveillance results.

Data that can be collected for this purpose are:

a. Additional data about MRSA colonised or infected patients (numerator):
    - Patient age and sex
    - Screening or clinical isolate
    - If infected patient: infection site(s) and infection date(s)
    - Antibiogram, genotype
b. Denominator data:
    - Number of patients admitted to the hospital / ward / unit that month
    - Number of patient-days that month in the hospital, and per ward/unit
    - Total number of *S. aureus* isolated from clinical samples, preferentially counted once per patient-admission

Four indicators can be calculated for the given time period:

1. The proportion of methicillin-resistance in *S. aureus* (sometimes referred to as "resistance rate") = Number of MRSA*100/ Number of SA, where preferentially patients are counted only once per hospitalisation and screening samples are excluded.
2. Incidence rate: Number of new nosocomial MRSA cases/ 1,000 admissions in the hospital and per ward/unit.
3. Incidence density: Number of new nosocomial MRSA cases/ 1,000 patient-days in the hospital and per ward/unit.
4. Ratio of new nosocomial MRSA cases/new imported MRSA cases.

This ratio indicates the importance of nosocomial transmission related to MRSA imported from the community, re-admissions, nursing homes or other institutions. A ratio lower than 1 indicates that more than half of the MRSA cases in the hospital arrive from outside.

This ratio is influenced by the policy of screening on admission but may still provide a good indicator of nosocomial transmission in the hospital and the wards. Other methods of studying transmission of MRSA in hospitals may be considered as well[41].

The incidence of nosocomial MRSA bacteraemia is an important and robust indicator of the overall attack-rate of MRSA infection and makes it possible to assess the clinical impact of MRSA.

To assess the relative importance of nosocomial MRSA infections, the prevalence of specific MRSA infections should be determined per body site (e.g. percentage of infections of surgical wounds, bacteraemia).

Benchmarking of the MRSA problem can be performed by participating to the national MRSA surveillance project organized since July 1994 by GDEPIH/GOSPIZ, the Institute of Public Health and the Staphylococci reference laboratory (ULB, M. Struelens). It allows participants:

1. to compare their own incidence and resistance indicators either to those from other participating hospitals of similar size or by region;

2. to validate their MRSA detection methods and to obtain strain characterisation, by transmitting MRSA strains to the Reference Laboratory (ULB).

5 Identification of MRSA reservoirs

5.1 When to search for MRSA reservoirs

The main reservoirs of MRSA in the hospital are colonised or infected patients, chronic MRSA carriers among members of staff and to some extent the environment. Identifying in-hospital MRSA reservoirs serves a triple purpose: (1) to yield a better understanding of the modes of transmission, (2) to quickly identify and isolate potential source patients and (3) to decontaminate the reservoirs.

When the incidence of MRSA infection and/or colonisation increases significantly in clusters, be it in one or several hospital wards, an outbreak investigation must be undertaken in order to elucidate the source(s) and mode(s) of transmission.

On the one hand, the hospital hygiene team must set up a descriptive epidemiological study of "epidemic" cases by reviewing the clinical files of the patients colonised and/or infected by MRSA and their characteristic variables: person, time and place. In particular, the type of pathology, hospital ward, diagnostic and therapeutic procedures preceding the acquisition of MRSA must be assessed.

On the other hand, it is advised that the laboratory keep a set of MRSA isolates (minimum 10) from different patients and send it to a reference laboratory for epidemiological typing (genotyping by pulsed-field gel electrophoresis and additional methods as appropriate). If the majority of these isolates appear identical or very closely related one can assume that the epidemic is clonal and that nosocomial transmission is probable. In case of type diversity (multiple clones), it is more likely that at least part of the MRSA patients became colonised in other healthcare institutions before their admission to the given hospital. However, due to the limited number of epidemic clones that disseminate throughout the country, the clonal character of an epidemic can be difficult to establish.

It might be useful to sub-type MRSA strains of a major epidemic clone with markers unrelated to DNA (e.g. phage typing) in order to recognize national or local epidemic sub-types reflecting small scale evolutions.

When case analysis and typing indicate local transmission of an epidemic clone, continuous screening (e.g. weekly) of the patients colonised by MRSA can be useful to rapidly isolate and/or decontaminate carriers as well as infected patients in that ward or institution.

Screening the MRSA status of patients on admission can be indicated in particular situations:

1. When epidemiological analysis indicates that a substantial number of MRSA cases are transferred to the hospital on a regular basis from other institutions where MRSA are (suspected to be) endemic, it might be safe to screen incoming patients systematically in order to detect MRSA colonisation as soon as possible and nurse the patients accordingly.
2. In case of an outbreak, screening may differentiate "imported cases", or re-admissions of colonised patients (positive culture within 48 hours after admission) from new cases of nosocomial colonisation or infection (positive culture later than 48 hours after admission). This differentiation allows for an improved assessment of the efficacy of control measures.
3. If case analysis and typing indicate that colonised patients are imported into a ward, screening on admission to this ward makes it possible to isolate and/or decontaminate these patients. Such systematic screening is particularly recommended in units where patients are at high risk of serious MRSA infections (intensive care units, heart surgery, major surgery such as organ transplantation).
4. When the incidence of serious MRSA infections in a care unit and/or a surgical department is high and cannot be controlled by patient isolation and/or decontamination, an analytical epidemiological study (case-control or cohort type) can be useful to identify a possible common source (staff or environment). In that case, it is necessary to obtain microbiological confirmation (culture and typing) about which carriers/disseminators and/or contaminated material are the source of the infections in order to target decontamination.

5.2 Detection of MRSA colonised and/or infected patients and staff

Identifying MRSA colonised and/or infected patients and staff is a capital step in the detection and management of MRSA epidemics. Screening patients leads to unknown carriers being identified earlier and reduces the risk of exposure through early isolation and decontamination. Although less

essential, it may be useful in specific circumstances to identify chronic MRSA carriers among staff in order to eradicate epidemics caused by “human disseminators”. In any case, screening for MRSA carriers is cumbersome, time consuming and costly. Therefore, a reliable strategy on the time, place, target and methods of MRSA screening is necessary.

5.2.1 General technical considerations

Screening for MRSA carriage is generally performed by swabbing the suspected anatomical site and performing a selective culture in the microbiology lab. Sterile cotton or Dacron swabs can be used. If cotton swabs are used, carbon-impregnated swabs are preferred[42]. Although advised for many years, it is not clear whether humidifying the swab before taking the sample increases the sensitivity of detection.

In spite of the lack of supporting evidence, the use of a Stuart’s transport medium and storage at ±4°C until inoculation may increase the recovery of MRSA[42]. To increase the yield by 30 to 50 %, an enrichment medium can be used.

5.2.2 Detection of MRSA carriers among patients

The need (number of sites tested, techniques) for screening hospital patients for MRSA largely depends on the objectives and available resources. The simplest, fastest and most cost-effective technique uses a nasal swab from the two anterior nostrils[43,44] but nasal swabs, even when performed properly only detect 78 to 85% of the carriers[45,46]. To perform the nasal culture, the swab must be rolled in both of the anterior nostrils.

An additional swab of the throat increases detection performance to 86%[46]. Combined samples from the nose, throat and perineum increases the sensitivity to more than 98%.

Additional samples may be indicated in specific situations:
- sputum of patients with productive cough, tracheotomy or when ventilated;
- urine when there is a bladder catheter;
- all wound or skin lesions;
- gastrostomy and suprapubic bladder insertion sites;
- catheter insertion sites.

5.2.3 Demonstration of MRSA eradication of known carriers

Samples must be taken at least 48 hours after the last antibiotic dose was administered or after decontamination.

All of the following body sites must be cultured:
- all previously contaminated or infected sites;
- anterior nostrils;
- throat;
- sputum of patients with productive cough, tracheotomy or when ventilated;
- urine when bladder catheter is present;
- all wound or skin lesions;
- all catheter insertion sites.

In order to demonstrate eradication of MRSA carriage it is necessary to repeat the screening procedures 3 times[47].

5.2.4 Detection of MRSA colonisation among staff

In an epidemic or when a local cluster of cases arises that cannot be controlled by the preventive measures described, one must search for persistent MRSA colonisation among the healthcare workers. This is particularly important when there are surgical site infections as a result of per-operative contamination. When this is the case, it is advisable to rapidly screen (culture nose and throat) the clinical staff in these units. When persistent colonisation is demonstrated, a confidential medical interview should be conducted to rule out chronic inflammatory conditions that favour colonisation and airborne dispersal of MRSA. Such conditions, which include chronic dermatitis, bronchitis or sinusitis, have previously been implicated in common-source outbreaks.

Some healthcare workers are at higher risk for MRSA carriage, especially doctors and nurses who attend to MRSA patients or patients at risk (open wounds, geriatric patients, etc). It must be emphasised that not only doctors and nurses, but also other healthcare workers and paramedics like students, ergotherapists, kinesitherapists/physiotherapists, radiology technicians, etc. have close contact with patients and, when indicated, must therefore be included in screening procedures.

In hospitals where extensive MRSA transmission occurs over long periods of time in many care units, screening and treating healthcare worker carriers is less effective compared to the considerable financial burden and workload. In that case, the cost and effectiveness of this approach must regularly be re-assessed.

Screening hospital staff for MRSA aims at detecting persistent nasal carriage and colonisation of skin lesions. In order to detect nasal carriage, a swab of both anterior nostrils is carried out when the members of staff start their shifts, thus avoiding the detection of transient carriage. Persistent nasal carriage is established by two positive cultures obtained within a time-span of 24 hours or more.

Standard practice should be to sample the nose and throat. Sampling and processing may be simplified by using a single swab: first perform a throat swab, then use the same swab to perform a nasal swab. A perineal swab is indicated when a healthcare worker is shown to carry MRSA repeatedly. Any skin lesion, even a minor one on the hands, is sampled by swabbing and cultured with an enrichment medium.

Belgian regulations are unclear in regard to the responsibility of the hospital hygienists and the occupational health doctor. Screening hospital workers for MRSA can either be organised by the occupational health doctor or the hospital hygiene doctor, but strict confidentiality regarding the results must be guaranteed.

5.2.5 Method of in vitro culture

Enrichment is strongly recommended[48,49] for sensitive detection of MRSA carriage since it may increase the recovery rates by 30 up to 50% in comparison to solid media alone. An acceptable method is to inoculate a (tryptic soy) broth supplemented with 7.5% NaCl and to incubate it at ±37°C for 18 hours minimum. The inoculated broth is subsequently sub-cultured onto solid media: blood agar plate and (optional) phenol-mannitol agar.

One can either use selective enrichment (containing salt and/or antibiotics) and subsequently non-selective solid media, or non-selective enrichment followed by inoculation on selective solid media (e.g. mannitol salt agar supplemented with 4 to 6 mg/L of oxacillin). Note that solid selective media should be incubated for 48 hours[50].

In general, liquid media yield better results (higher sensitivity) than solid media[48,49].

The salt concentration to be used in liquid media remains controversial. Although a NaCl concentration > 2.5% can inhibit some strains of endemic MRSA[51], the Hospital Infection Society[52] and American Society for Microbiology[49] recommend 7,5% NaCl (in Brain Heart Infusion and MSA respectively).

Selective growth can be performed with antibiotics. Oxacillin or the combination of 75 mg/L of aztreonam and 5 mg/L of ceftizoxime[53] can be used. The latter combination enhances the expression of oxacillin-resistance in *S. aureus*.

The main limitation of broth-enriched MRSA screening cultures is the delay of about 4 to 5 days between sampling and final reporting. PCR detection of MRSA in selective enrichment broth or directly on clinical specimens reduces this delay to 12- 36 hours. The cost-effectiveness of this approach is under investigation.

6 Decontamination of reservoirs

6.1 Decontamination of hospitalised patients

Colonised patients constitute the main reservoir of MRSA in the hospital and a frequent source of contamination of the staff. Secondly, it is preferable to nurse MRSA patients in isolation, which constitutes a serious burden both to the patient and to the hospital and healthcare workers. Therefore, no effort must be spared in an attempt to decontaminate patients from MRSA.

Topical treatment of patients colonised or infected at muco-cutaneous sites other than bronchial mucosa allows either its eradication (nasal carriage), or reduction in intensity (other sites). The simplest, most efficient and safest treatment combines the application of a mupirocin nasal ointment (3 x/day in the anterior nostrils) and body wash (including skin lesions) with an antiseptic soap (chlorhexidine or polyvidone-iodine based) once a day for 5 days. Although this regimen is very successful in eradicating MRSA from > 98% of healthcare workers, decontamination of patients is often difficult or impossible. Especially geriatric patients with contaminated wounds or colonisation of the respiratory tract or patients with indwelling devices or gastrostomy seem to be much more difficult to decontaminate. Even without chronic respiratory carriage, nasal mupirocin combined with antiseptic body wash results in only a minority of patients (25%) with multiple body site colonisations being rid of MRSA[31]. Some other patients may be re-colonised with MRSA, possibly due to persistent intestinal carriage. Those cases should be treated again with the same regimen. Although oral administration of vancomycin was proven effective in terminating one MRSA outbreak in an ICU[54] it is generally unacceptable because of the risk of vancomycin resistance emerging among enterococci and *S. aureus*.

The in-hospital use of a mupirocin-based skin cream should be restricted, particularly in cases of chronic lesions or lesions associated with foreign bodies, in order to reduce the risk of mupirocin resistance emerging and disseminating.

Decontamination of mupirocin resistant strains can be achieved with mupirocin in about half of the cases.

Other decolonisation regimens have been described with limited success but can be an alternative: among others, topical decontamination with povidone-iodine[55], tea tree oil[56] or nitrofurazone (Furacine®) have been reported successful[57,58]. Oral administration of novobiocin-rifampin[59], systemic administration of co-trimoxazole and fusidic acid[60] or minocycline and rifampin has been proven effective in some instances. Overall, systemic use of antibiotics is only of limited value due to the low success rate and rapid emergence of resistance but can be considered in exceptional situations after repeated failure of the standard decontamination procedure.

6.2 Decontamination of hospital staff.

Epidemiological investigation and strain typing may, in exceptional situations, identify a member of the hospital staff as the probable common source of MRSA infections. Persistent MRSA carriers among the staff should be informed and decontaminated with an identical regimen. If the topical treatment should fail, an oral antibiotic treatment can be used. Skin disorders (eczema, contact dermatosis, ...), which foster chronic carriage and the dispersal of MRSA, must be sought and treated when present.

6.3 Decontamination of the hospital environment.

Common practice for cleaning and disinfecting premises and medical equipment is applicable in care units where patients colonised or infected by MRSA are treated. Standard methods are generally appropriate to prevent the transmission of these organisms from the environment. Cleaning is done every day and after discharge of such patients. A check-list can be supplied to the cleaning staff to ensure that the surfaces manipulated or directly exposed to contaminated material are carefully cleaned. In exceptional cases, when an epidemiological investigation identifies fomites or medical equipment (respirator, X-ray table...) as the common source of MRSA infection, specific decontamination of this equipment may be required.

7 Additional barrier precautions

7.1 General considerations

The transmission of MRSA can be kept within bounds by taking both standard (or general) precautions and specific additional precautions (individual room and use of gloves, gown and mask).

Among the standard procedures, strict hand-hygiene practices need to be actively promoted and implemented, compliance with these practices evaluated and feedback of the observation delivered to the healthcare workers[61].

A written document must be available for all hospital staff stating clearly which additional precautions must be taken when patients colonised or infected by MRSA are approached. An active information programme and programme overlooking compliance with the recommended precautions should be implemented.

One should consider applying additional MRSA procedures until the screening tests produce negative results when attending to any formerly known MRSA carrier or patient at risk for MRSA colonisation, or transferred from a ward or other healthcare institute with a known or suspected high incidence of MRSA infection.

7.2 Nursing precautions

Ideally, all patients carrying MRSA in any site other than the nostrils (as this limited carriage can be eradicated effectively with nasal mupirocin) are nursed in an individual room equipped with sanitary installations and medical equipment (thermometer, stethoscope) specific to the patient. A card mentioning the measures to be taken must be clearly visible before entering the room. Barrier precautions must be applied whenever the patient leaves the room.

It is difficult to determine precisely at which point in time these additional precautions can be lifted. In practice, isolation can be lifted when three sets of consecutive cultures carried out at a few days' interval fail to grow MRSA.

When several patients carrying MRSA are identified and individual rooms are unavailable, the patients can be grouped in a common room (preferably in a restricted part of the unit). When possible, a limited number of healthcare workers should attend to these patients in order to decrease the population of staff exposed (cohort nursing).

Cohorting carriers in a dedicated ward effectively limits MRSA transmission and should be considered when other measures fail to improve the situation.

Healthcare workers should always wear gloves and gowns when entering the room if contact with the patient or the environment is anticipated. Gloves and gowns must be removed when leaving the room or in between procedures. In all cases the healthcare staff must disinfect their hands after taking off their gloves.

Healthcare workers should always wear masks when performing procedures that can potentially generate aerosols (e.g. tracheal or bronchial aspiration, dressing of an infected wound, bed sheet change). This precautionary measure also reduces the risk of contact between hands and nose. Some epidemiological data suggest that wearing a mask can also be of benefit in other circumstances and should be suggested.

Visitors should be encouraged to decontaminate their hands after any contact with the patients and when leaving the room and should be encouraged to generally apply the healthcare workers' recommendations.

Visitors to more than one patient should apply all the additional MRSA measures proposed to the healthcare workers.

The linen and waste contaminated by MRSA does not constitute a medical hazard when linen treatment and waste disposal are carried out according to standard regulations.

Close attention is needed to cleaning and disinfecting high touch surfaces in patient care areas. Decontamination of the floor and horizontal surfaces of the room after discharge of the MRSA patient is recommended (see 6.3).

8 Follow-up of patients and communication within and between healthcare institutions

8.1 General considerations

Communicating data regarding the status of MRSA carriage of a patient must be done in accordance with the protection of confidentiality and patient privacy. The rapid identification of patients carrying MRSA by means of labels (e.g. coloured labels with a specific logo) applied on the medical and nursing file can constitute a useful measure.

8.2 Keeping the healthcare institution staff informed

It is necessary to plan the visits and consultations of carrier patients in the various wards or technical units (e.g. endoscopies, X-rays, operating department). All diagnostic procedures carried out in a unit other than that in which the patient is hospitalised, should also be organized by the nursing team in charge.

Medical and paramedical staff in technical units including the operating ward must be informed about the MRSA status of the patient. Written procedures about the precautions to be taken during visits and/or examinations carried out on patients carrying MRSA must be available. There must be particular insistence on the importance of wearing a protection coat and gloves for any direct contact with the patient and on the need for disinfecting one's hands with an antiseptic solution after contact with the patient.

Non-medical ambulance and welfare staff must also be informed about the precautions to be taken when a patient infected by MRSA is being transferred to another unit.

8.3 Identification and follow-up of patients on admission

For some individuals, MRSA carriage can persist for a long time (several months and even several years). When such patients are re-admitted to the hospital, they constitute a significant source from which this micro-organism can be re-introduced there. Consequently, it seems important to be able to identify these patients as soon as possible.

The following methods must be applied:

- Maintaining a (electronic) registry of MRSA carriers from the laboratory information system.
- Systematic printing or electronic reporting of a laboratory protocol of any new patient carrying MRSA as an alert notified in the medical record. A copy is to be sent to the infection control team.
- Identification of MRSA carriers in the hospital information system in order to allow special precautions to be taken upon re-admission.

Preventive isolation precautions may also be considered for patients known as former MRSA carriers as well as for those presenting specific risk factors for MRSA carriage on admission. This target group includes patients hospitalised for more than 24 hours within the last 6 months, and especially those with open wounds, recent surgery, presence of long term catheter or drainage, intubated patients, and those transferred from hyper endemic institutions.

8.4 Transfer between healthcare institutions and post-discharge follow-up

Any transfer to another hospital of a patient carrying MRSA must be previously notified to the doctor in charge by telephone or letter explaining the transfer. It is also recommended that a standard transfer document be available in each hospital. This document must be completed when the patient leaves the hospital and can be addressed (together with the patient) to the physician in charge in the receiving healthcare institution. It is suggested that a standard document be developed in collaboration between several acute care hospitals and long term care facilities through the Regional Platforms for healthcare infection control. This document should at least contain a list of the colonised sites, local and/or systemic treatment administered to the patient and the microbiological status of the patient at discharge. It is recommended to report to the physician in charge patients colonised or infected by MRSA that leave the hospital to be transferred to convalescence or nursing homes.

To minimise the risk of MRSA transmission by contacts with the patients and their families during transfer between healthcare facilities, it is recommended to provide clear information to the patients and their relatives about the significance of MRSA carriage and the precautions to be taken to limit its dissemination. To this end, distributing a written document to the patients and their relatives can facilitate communication.

When a MRSA colonised or infected patient leaves the hospital to receive ambulatory care, it is recommended that the general practitioner be fully informed of the follow-up of MRSA colonisation or infection through the discharge medical report and any additional standard document.

9 List of recommendations

The table summarizes the recommendations proposed in the text and attributes a category of priority for implementation:

I. Recommended for all hospitals
II. Probably useful for all hospitals
III. Recommended in specific situations
IV. Probably not useful

	Intervention	Ref. in text	Priority
Chapter 3. Identification of MRSA and susceptibility testing for oxacillin-resistance			
	Confirmation of oxacillin-resistance with another test than the screening test at least once per patient and in case of any atypical results or discrepancy	3.2.2	I
	Confirmation of oxacillin-sensitivity on MSSA with resistance to fluoroquinolones, aminoglycosides or tetracyclines	3.2.1	I
	In vitro susceptibility determination of vancomycin and/or teicoplanin on MRSA.	3.3	I
	Rapid presumptive identification with latest-generation latex agglutination	3.1	II
	Routine detection of oxacillin-resistance with agar diffusion (oxa-1 or cefoxitin disc) or oxa-screen agar		II
	Identification of *S. aureus* with coagulase test	3.1	III
	Demonstration of the *mecA* gene by means of PCR	3.2.2	III
	Demonstration of the presence of PBP2a with a latex agglutination test	3.2.2	III
	In vitro detection of low-level and high-level resistance to mupirocin on MRSA.	3.3.1	III
	Screening for GISA with the agar screen technique on clinical isolates of MRSA	3.3.2	III
	Screening for hGISA with the agar screen technique on clinical isolates of MRSA	3.3.2	III
Chapter 4. Epidemiological investigation and follow-up of MRSA in the institution.			
	Set up a continuous surveillance of MRSA based upon data from their microbiology laboratory	4.1	I
	Continuous or periodical participation to the national surveillance of MRSA	4.2	II
	Allow for a timely response to an increase in the incidence of MRSA cases in the different wards	4.1	I
	Report on a monthly basis the number of new patients colonised and/or infected by MRSA for each ward/unit	4.1	II
	Distribute feed-back to heads of the wards and head physician	4.1	II
	Discuss the results with the ward/unit staff concerned	4.1	II
	In-depth epidemiological analysis of the MRSA problem	4.2	III

Legend: I: Recommended for all hospitals; II: Probably useful for all hospitals; III. Recommended in specific situations; IV: Probably not usefull

	Intervention	Ref. in text	Priority
Chapter 5. Identification of MRSA reservoirs			
	Minimum sample for MRSA screening is selective culture of both anterior nostrils	5.2.2	I
	Additional throat swabs are advised for MRSA screening	5.2.2	I
	Additional sample of sputum of patients with productive cough, tracheotomy or when ventilated is advised for MRSA screening	5.2.2	I
	Additional sample of urine when bladder catheter is present is advised for MRSA screening	5.2.2	I
	Additional sample of all wound or skin lesions when present is advised for MRSA screening	5.2.2	I
	Additional sample of gastrostomy and suprapubic bladder insertion sites is advised for MRSA screening	5.2.2	I
	In order to demonstrate eradication of MRSA carriage it is necessary to repeat the screening procedures 3 times, awaiting the result before the next sampling	5.2.3	I
	When screening the staff is indicated, samples of nose and throat must be obtained.	5.2.4	I
	Additional sample of catheter insertion sites is advised for MRSA screening	5.2.2	II
	Screening the MRSA status of patients on admission when epidemiological analysis indicates that a substantial number of MRSA cases are being transferred to the hospital	5.1	II
	Screening the MRSA status of patients on admission to hospital or ward in case of an epidemic	5.1	II
	Use an enrichment medium for MRSA screening	5.2.5	II
	Additional perineal swabs are advised for MRSA screening	5.2.2	III
	Perform outbreak investigation	5.1	III
	Set up a descriptive epidemiological study of "epidemic" cases by reviewing the clinical files of the patients	5.1	III
	The laboratory keeps a set of MRSA isolates from different patients and sends it to a reference laboratory for epidemiological typing	5.1	III
	Continuous screening (e.g. weekly) of the patients colonised by MRSA	5.1	III
	Perform an analytical epidemiological study (case-control or cohort type)	5.1	III
	In an epidemic or when a local cluster of cases arises that cannot be controlled by the preventive measures described, one must search for persistent MRSA colonisation among the healthcare workers	5.2.4	III
Chapter 6. Decontamination of reservoirs			
	Standard regimen for decontamination takes 5 days and consists of intranasal application of an antistaphylococcal agent and body wash with an antiseptic soap.	6.1	I
	MRSA colonised healthcare workers should be decontaminated	6.2	I
	Standard methods for cleaning and disinfecting premises and medical equipment are generally appropriate to prevent the transmission of these organisms from the environment	6.3	I
	MRSA colonised or infected patients should be decontaminated	6.1	III

Legend: I: Recommended for all hospitals; II: Probably useful for all hospitals; III. Recommended in specific situations; IV: Probably not usefull

	Intervention	Ref. in text	Priority
Chapter 7. Additional barrier precautions.			
	Strict hand-hygiene practices need to be actively promoted and implemented, compliance with these practices evaluated and feedback of the observation delivered to the healthcare workers	7.1	I
	A written document must be available for all hospital staff stating clearly which additional precautions must be taken when patients colonised or infected by MRSA are approached	7.1	I
	Healthcare workers should always wear gloves and gowns when entering the room if contact with the patient or the environment is anticipated.	7.2	I
	Healthcare staff must disinfect their hands after taking off their gloves when attending to MRSA patients	7.2	I
	Healthcare workers should always wear masks when performing procedures that can potentially generate aerosols	7.2	I
	Visitors to more than one patient should apply all the additional MRSA measures proposed to the healthcare workers	7.2	I
	All patients carrying MRSA in any site other than nostrils are nursed in an individual room equipped with sanitary installations and medical equipment specific to the patient	7.2	II
	When several patients carrying MRSA are identified and individual rooms are unavailable, the patients can be grouped in a common room	7.2	II
	Cohorting carriers in a dedicated ward effectively limits transmission of MRSA and should be considered when other measures fail to improve the situation.	7.2	II
	Decontamination of the room after discharge of the MRSA patient	7.2	II
	Additional MRSA procedures must be applied until the screening tests produce negative results when attending to any formerly known MRSA carrier or patient at risk for MRSA colonisation, or transferred from a ward or other healthcare institute with a known or suspected high incidence of MRSA infection	7.1	III
Chapter 8. Follow-up of patients and communication within and between healthcare institutions			
	Visits and consultations of carrier patients in the various wards or technical units must be planned	8.2	I
	Medical and paramedical staff in technical units including the operating ward must be informed of the precautions to be taken during visits and/or examinations carried out on patients carrying MRSA	8.2	I
	There must be particular insistence on the importance of wearing a protection coat and gloves for any direct contact with the patient and on the need for disinfecting one's hands with an antiseptic solution after contact with the patient	8.2	I
	Non-medical ambulance and welfare staff must also be informed of the precautions to be taken when a patient infected by MRSA is being transferred to another unit	8.2	I
	Any transfer to another hospital of a patient carrying MRSA must be previously notified to the doctor in charge by telephone or letter explaining the transfer	8.4	I
	A standard transfer document must be available in each hospital.	8.4	I
	The patient and his relatives must be informed about the significance of MRSA carriage and the precautions to be taken to limit dissemination	8.4	I
	Patients carrying MRSA must rapidly be identifiable by means of labels on the medical and nursing file	8.1	II
	All diagnostic procedures carried out in a unit other than that in which the patient is hospitalised, must be organized by the nursing team in charge.	8.2	II
	Patients colonised or infected by MRSA that are transferred to convalescence or nursing homes must be reported to the physician in charge	8.4	II

Legend: I: Recommended for all hospitals; II: Probably useful for all hospitals; III. Recommended in specific situations; IV: Probably not usefull

	Intervention	**Ref. in text**	**Priority**
	When a MRSA colonised or infected patient leaves the hospital to receive ambulatory care, it is recommended that the general practitioner be fully informed of the follow-up of MRSA colonisation or infection through the discharge medical report and any additional standard document	8.4	II
	Patients recently hospitalised for more than 24 hours or transferred from another hospital or presenting risk factors for MRSA colonisation must be isolated.	8.3	III

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