Impact of routine surgical ward and intensive care unit admission surveillance cultures on hospital-wide nosocomial methicillin-resistant 
Staphylococcus aureus infections in a university hospital: an interrupted time-series analysis

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Objectives: To determine whether a routine admission screening in surgical wards and intensive care units (ICUs) was effective in reducing methicillin-resistant Staphylococcus aureus (MRSA) infections—particularly nosocomial MRSA infections—for the whole hospital.

Methods: The study used a single-centre prospective quasi-experimental design to evaluate the effect of the MRSA screening policy on the incidence density of MRSA-infected/nosocomial MRSA-infected patients/1000 patient-days (pd) in the whole hospital. The effect on incidence density was calculated by a segmented regression analysis of interrupted time series with 30 months prior to and 24 months after a 6 month implementation period.

Results: The MRSA screening policy had a highly significant hospital-wide effect on the incidence density of MRSA infections. It showed a significant change in both level (−0.163 MRSA-infected patients/1000 pd, 95% confidence interval (CI): −0.276 to −0.050) and slope (−0.01 MRSA-infected patients/1000 pd per month, 95% CI: −0.018 to −0.003) after the implementation of the MRSA screening policy. A decrease in the MRSA infections by 57% is a conservative estimate of the reduction between the last month before (0.417 MRSA-infected patients/1000 pd) and month 24 after the implementation of the MRSA screening policy (0.18 MRSA-infected patients/1000 pd). Equivalent results were found in the analysis of nosocomial MRSA-infected patients/1000 pd.

Conclusions: This is the first hospital-wide study that investigates the impact of introducing admission screening in ICUs and non-ICUs as a single intervention to prevent MRSA infections performed with a time-series regression analysis. Admission screening is a potent tool in controlling the spread of MRSA infections in hospitals.

Keywords: MRSA, screening policies, infection control, prevention measures, reduction

Introduction

A steadily increasing number of patients treated in hospitals are colonized or infected with antibiotic-resistant bacteria. Preventing the spread of these pathogens while providing optimal treatment for patients is a major challenge. Methicillin-resistant Staphylococcus aureus (MRSA) is currently probably the most important of these bacteria, and the management of MRSA infections and the prevention of their nosocomial transmission are a central problem of hospital epidemiology.1,2

A significant increase in MRSA case patients has also been recorded in German hospitals within the last 5 years.3 MRSA acquisition is highly associated with subsequent infection in hospital.4 Several studies have demonstrated the burden and the economic impact of MRSA infections in the hospital setting.5–8 Hospital-acquired MRSA infections are associated with increased morbidity and mortality, with the prolongation of hospital stay and attributable total and direct costs.9–13 Hence, the development of a comprehensive strategy to prevent nosocomial MRSA infections is imperative.14

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The source of spread of MRSA can be likened to an iceberg, with clinically obvious infections representing the tip of the iceberg and most of the spread coming from clinically inapparent colonized patients who represent most of the reservoir for transmission. Surveillance cultures to identify this reservoir are important for the control of spread with effective barrier precautions. Such precautions have been shown to reduce the spread of MRSA. Moreover, several studies have shown successful reduction of nosocomial MRSA infections by implementing an admission screening in intensive care units (ICUs).

Despite the existence of an established infection control programme combating MRSA including effective barrier precautions such as isolation measures in single rooms, alerting known readmitted patients and screening of roommates, a steady increase in nosocomial MRSA infections was noted at Hannover Medical School in 2004. Hence, an extended admission screening policy in surgical wards and ICUs housing the largest number of risk patients was established mid-2004.

The aim of this study was to determine whether an admission screening on surgical wards and ICUs was effective in reducing nosocomial MRSA infections for the entire hospital.

Materials and methods

Study design and setting

The study used a single-centre prospective quasi-experimental design with a segmented regression analysis of interrupted time series, according to the guidelines of the ORION statement.

Hannover Medical School is a 1400 bed university hospital that includes 129 intensive care medicine beds and 212 beds for the major surgical departments such as trauma, visceral and thoracic cardiovascular surgery in Germany. Thus, a total of 341 beds were included for intervention in this study. The main focus of the hospital is on transplantation medicine. Nearly 45 000 inpatients with about 400 000 patient-days (pd) are treated every year including ca. 12 000 surgical patients.

Surveillance and data

The previously described method for prospective MRSA surveillance was established at our hospital in the year 2001. In brief, the following definitions were used for this ongoing surveillance. MRSA-positive case patients included all hospitalized patients from whom MRSA was isolated from clinical samples or from screening cultures during their stay as well as hospitalized patients with known clinical evidence of MRSA infection or colonization. Every hospital stay for an MRSA-positive case patient was recorded as a separate case of MRSA infection or colonization, no matter how many times the patient was known to have been admitted previously. Patients whose clinical diagnostic specimens or screening culture samples yielded one or more isolates of MRSA were classified as having MRSA colonization. Patients who had clinical signs and symptoms of infection and who had provided a sample identified as MRSA positive from a corresponding culture were classified as having MRSA infection. In the case of doubt, the decision about whether the patient actually had an MRSA infection was made by the treating physician.

MRSA infection or colonization was considered nosocomial if the positive clinical specimen or screening culture sample was obtained >48 h after the patient’s admission to the hospital, and no previous culture result positive for MRSA was available. All remaining cases of MRSA infection or colonization were defined as imported.

In addition, every MRSA case patient was evaluated whether he/she had developed a nosocomial MRSA infection based on an existing MRSA colonization during his/her hospital stay.

To assess the extent of the screening regime, the total number of nares cultures was recorded (one culture per patient; multiple cultures of samples from the same patient were excluded).

Monthly total patient-days were obtained from the hospital administration system and aggregated for the calculation of incidence density.

When multiple clinical isolates were obtained from a given patient, duplicates were eliminated.

Population, infection control policies and resources

Figure 1 gives details of the population, infection control policies and resources throughout the study, during which only the admission screening policies changed.

Intervention and outcome

Admission screening for MRSA carriage was introduced into the wards with the main MRSA problem, i.e. the adult surgical wards (trauma, visceral and thoracic cardiac vascular surgery) and adult ICUs, in July 2004.

The primary outcome measure was the incidence of all MRSA infections. Secondary outcome was the incidence of nosocomial MRSA infection.

Microbiology methods

Throughout the study period (January 2002 to December 2006), all clinical specimens were processed by the standard culture methods on Columbia 5% sheep blood agar (BBL Microbiology Systems, Becton Dickinson, Heidelberg, Germany) and mannitol salt agar (own production). After 24 h of incubation at 36°C, colonies that had morphology consistent with S. aureus were evaluated by Gram stain, catalase test and coagulase test (Staphyslide-test, bioMérieux, Marcy l’Étoile, France).

The antibiotic susceptibility of S. aureus isolates was measured by broth microdilution with the MICRONAUT™ system (Merlin Diagnostika GmbH, Hersel, Germany). Susceptibility interpretations were made according to breakpoints in accordance with the CLSI (formerly the NCCLS) guidelines.

Screening swabs were cultured directly onto a selective culture medium (MRSA ID-Agar™, bioMérieux) only from July 2004 to December 2006. MRSA isolates were confirmed with a slide latex agglutination kit to detect penicillin-binding protein 2a (PBP2 Latex Agglutination Kit, bioMérieux).

Data analysis

Starting from January 2001, the number of pd and MRSA patients (stratified by colonized, infected and nosocomially infected patients) were collected prospectively for the entire hospital and stored in a database by the infection control nurses. The validity of these MRSA data was assessed by continuous reviewing of the infection control nurses by one physician. Monthly incidence densities of MRSA-infected patients/1000 pd were calculated as the number of patients with any MRSA infection event in a given month, divided by the number of pd for that month and multiplied by 1000.
Additionally, the incidence densities of MRSA patients and nosocomial MRSA-infected patients per 1000 pd were calculated.

We used the segmented regression analysis of interrupted time series to assess the changes in the MRSA-incidence density before and after the intervention (i.e. implementation of the screening programme).\textsuperscript{20,23} Level and slope are the two parameters that define each segment of a time series. The level is the value of the series at the beginning of a given time interval and slope is the rate of change of a measurement during a segment; in our analysis, there was a monthly (month-to-month) change. An abrupt intervention effect constitutes a drop or jump in the level (a change in the level) of the outcome after the intervention. The slope represents a gradual change in the outcome parameter during the segment. The method is described in greater detail elsewhere.\textsuperscript{24 – 26}

For the statistical analysis of monthly incidence densities, we analysed 30 monthly time points before (January 2002–June 2004) and 24 monthly time points after (January 2005–December 2006) the intervention. The implementation period (July–December 2004) was not considered in the analysis.

The full segmented regression model included the baseline level and all levels and trend changes; slope before the intervention and change in the level and slope after the intervention were calculated. Therefore, non-significant variables were removed in a stepwise fashion for entry in the model with $P$ in 0.05 and $P$ out 0.10.

### Major infection control changes during the study:
Change from a mere routine screening of roommates and patients with a past history of MRSA (Phase 1) to a routine admission screening on surgical wards and ICUs housing the largest number of risk patients (Phase 2)

<table>
<thead>
<tr>
<th>Screening policy</th>
<th>Audit and feedback</th>
<th>Isolation policy MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 months (1 January 2002 to 30 June 2004)</td>
<td>Screening of roommates and known readmitted patients</td>
<td>Half-yearly feedback of total number of MRSA case patients and nosocomial MRSA infections to all departments housing MRSA patients</td>
</tr>
<tr>
<td><strong>Implementation period:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months (1 July 2004 to 31 December 2004)</td>
<td>As Phase 1 plus screening of all admitted patients on surgical wards and ICUs</td>
<td>As Phase 1</td>
</tr>
<tr>
<td><strong>Phase 2:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months (1 January 2005 to 31 December 2006)</td>
<td>As Phase 1 plus screening of all admitted patients on surgical wards and ICUs</td>
<td>As Phase 1</td>
</tr>
</tbody>
</table>

### Isolation details (all phases):
MRSA-positive patients were isolated in single rooms or cohorted in shared rooms if no single rooms were vacant. At least two single rooms were available on each ward including ICUs. Wall-mounted alcohol hand rub dispensers were installed in or in front of each room. In addition, disposable hand rub dispensers were provided in front of each isolation room. Hand-washing facilities were available with one to three sinks in every patient’s room together with unmedicated liquid soap and paper towels.

### MRSA screening policy (all phases):
Specimens for cultures were taken from both anterior nares by using one sterile swab and throat by using another one. Additionally, swabs were taken from existing wounds. No pre-emptive isolation procedures of screened patients were initiated prior to microbiological results, generally 48 h after culture was performed.

### MRSA eradication policy (all phases):
MRSA patients with prospective elective operation procedures were mainly decontaminated by intranasal mupirocin and antiseptic body washes, shampoo and gargling. Clearance is defined as three consecutive negative daily swabs from patient’s previously MRSA-positive sites, and no appropriate antimicrobial therapy was given.

### Definition of nosocomial MRSA acquisition (all phases):
Cases found on screening or clinical specimens taken >48 h after admission

### Definition of MRSA infection (all phases):
Patients with clinical signs and symptoms of infection and positive corresponding MRSA culture

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**Figure 1.** Population, clinical setting, nature and timing of admission screening and infection control interventions. ICU, intensive care unit; ICD, infection control doctor; ICN, infection control nurse; WTE, whole time equivalent.

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Impact of admission screening for MRSA

Table 1. Hospital demographics and incidence densities per 1000 pd of MRSA and of performed nares cultures, 2002–06

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of patients</td>
<td>40 225</td>
<td>39 129</td>
<td>44 647</td>
<td>46 785</td>
<td>48 338</td>
</tr>
<tr>
<td>no. of pd</td>
<td>391 516</td>
<td>385 842</td>
<td>401 015</td>
<td>396 863</td>
<td>412 440</td>
</tr>
<tr>
<td>length of stay (days)</td>
<td>8.9</td>
<td>8.9</td>
<td>8.4</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Incidence densities per 1000 pd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA patients/1000 pd</td>
<td>0.56</td>
<td>0.80</td>
<td>1.47</td>
<td>1.49</td>
<td>1.64</td>
</tr>
<tr>
<td>MRSA-infected patients/1000 pd</td>
<td>0.26</td>
<td>0.29</td>
<td>0.40</td>
<td>0.25</td>
<td>0.18</td>
</tr>
<tr>
<td>nosocomial MRSA-infected patients/1000 pd</td>
<td>0.11</td>
<td>0.19</td>
<td>0.23</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>nares cultures/1000 pd</td>
<td>2.3</td>
<td>4.7</td>
<td>11.6</td>
<td>18.6</td>
<td>20.4</td>
</tr>
</tbody>
</table>

Variables were tested for normal distribution by the Shapiro–Wilk test, and first-order autocorrelation was tested using the Durbin–Watson statistic. A value of 2.0 for the Durbin–Watson statistic indicated that serial correlation was not detected. The goodness of fit of the model was evaluated with the determination coefficient, $R^2$, corresponding to the percentage of the variance of the observed time series explained by the model. Additionally, to compare proportions, the relative risk was calculated. All statistical tests were considered significant with a value $\leq 0.05$. Data were analysed using SPSS for Windows 12.0.

Results

Throughout the study period, 39 129–48 338 inpatients were treated at Hannover Medical School per year (for details, see Table 1). A total of 2371 MRSA case patients were observed in the whole hospital during the 5 years. The MRSA incidence density increased from 0.56 to 1.64 MRSA case patients/1000 pd. No MRSA outbreak was detected during the course of the study. The number of surveillance cultures (cultures of swabs from the nares) performed/1000 pd increased 9-fold during this period from 2.3 in 2002 to 20.4 nares cultures in 2006.

The results of the segmented regression analysis of time series evaluating the impact of the admission screening policy on the incidence density of MRSA-infected patients/1000 pd in the whole hospital are represented in Table 2. The implementation of admission screening was associated with a significant change in the level of $-0.163$ MRSA-infected patients/1000 pd ($95\%$ CI: $-0.276 \text{ to } -0.050$). Additionally, after an implementation period of 6 months, the admission screening was associated with a significant change in the slope after the intervention of $-0.010$ MRSA-infected patients/1000 pd ($95\%$ CI: $-0.018 \text{ to } -0.003$). The significant increased trend before intervention (monthly change before intervention 0.007, 95% CI: 0.003–0.012) was reversed into a decreased trend of $-0.003$ MRSA-infected patients/1000 pd after the implementation of admission screening.

The Durbin–Watson test (1.702) showed no evidence of serial correlation for these data, and the determination coefficient $R^2$ was 0.33.

According to the regression model, there was a decrease of 57% in the MRSA-infected patients/1000 pd between month 30 (0.417 MRSA-infected patients/1000 pd), the last month before intervention, and month 60 (0.180 MRSA-infected patients/1000 pd), the last month in the analysed post-intervention period. However, this is a conservative estimate of the reduction, because the trend before intervention was not considered in the months after intervention.

Equivalent results showed the analysis of incidence densities of nosocomial MRSA-infected patients/1000 pd (Table 2). The conservative estimate shows a reduction of 63% in the nosocomial MRSA-infected patients.

Figure 2 shows the changes in the hospital-wide incidence density of MRSA-infected patients throughout the study period. Figure 3 shows the changes in the hospital-wide incidence densities of all MRSA patients, MRSA-infected patients and nosocomial MRSA-infected patients during the whole study period.

Similar increases and decreases were observed in the percentage of MRSA bacteraemia (Figure 4). In 2004, the proportion of MRSA of overall microbiological isolates of S. aureus from blood cultures increased significantly from 25% in 2003 to 45% in 2004 (RR = 1.8; 95% CI: 1.20–2.69; $P = 0.005$). In the second year after the implementation of the routine admission screening, the MRSA percentage of bacteraemia significantly decreased to 29.9% in 2006 (RR = 0.67; 95% CI: 0.46–0.96; $P = 0.04$).

Discussion

For most patients, MRSA is merely a colonizing organism and can only be detected through active screening. Unknown MRSA carriers constitute the main reservoir and source of further spread following hospitalization. Several recent studies have shown the importance of surveillance cultures from patients at admission into ICUs in order to prevent MRSA transmission and subsequent nosocomial MRSA infections. Many studies of control strategies for MRSA have concurrently introduced multiple interventions. Hence, determining the relative contribution of each intervention has not been possible.

To the best of our knowledge, this is the first hospital-wide study that investigates the influence of admission screening in ICUs and non-ICU settings as a single intervention to prevent MRSA infections performed with a time-series analysis. In this non-randomized prospective cohort study, we observed a significant association between an extended admission screening
on ICUs and surgical wards and a decrease in hospital-wide MRSA infections. These findings were supported by the time-series analyses of MRSA infection incidence densities before and after the implementation of the admission screening policy.

Our main outcome was MRSA-infected patients/1000 pd because the admission screening policy is a potential bias for misclassification of nosocomial cases before and after the implementation of the screening policy (Figure 4). This

Table 2. Results of segmented regression analysis of interrupted time series evaluating the impact of the admission screening policy on the incidence density of MRSA-infected patients, nosocomial MRSA-infected patients and MRSA-positive patients per 1000 pd in the whole hospital

<table>
<thead>
<tr>
<th>Model coefficients</th>
<th>Coefficient</th>
<th>P value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRSA-infected patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>constant</td>
<td>0.195</td>
<td>&lt;0.001</td>
<td>0.188–0.271</td>
</tr>
<tr>
<td>slope before INT</td>
<td>0.007</td>
<td>0.001</td>
<td>0.003–0.012</td>
</tr>
<tr>
<td>change in level after INT</td>
<td>−0.163</td>
<td>0.006</td>
<td>−0.276 to −0.050</td>
</tr>
<tr>
<td>change in slope after INT</td>
<td>−0.010</td>
<td>0.007</td>
<td>−0.018 to −0.003</td>
</tr>
<tr>
<td><strong>Nosocomial MRSA-infected patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>constant</td>
<td>0.073</td>
<td>0.011</td>
<td>0.017–0.129</td>
</tr>
<tr>
<td>slope before INT</td>
<td>0.006</td>
<td>&lt;0.000</td>
<td>0.003–0.009</td>
</tr>
<tr>
<td>change in level after INT</td>
<td>−0.122</td>
<td>0.004</td>
<td>−0.204 to −0.040</td>
</tr>
<tr>
<td>change in slope after INT</td>
<td>−0.008</td>
<td>0.004</td>
<td>−0.013 to −0.003</td>
</tr>
<tr>
<td><strong>All MRSA patients (infected or colonized)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>constant</td>
<td>0.281</td>
<td>0.001</td>
<td>0.119–0.444</td>
</tr>
<tr>
<td>slope before INT</td>
<td>0.034</td>
<td>&lt;0.001</td>
<td>0.026–0.042</td>
</tr>
<tr>
<td>change in level after INT</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change in slope after INT</td>
<td>−0.015</td>
<td>0.002</td>
<td>−0.032–0.001</td>
</tr>
</tbody>
</table>

We analysed 30 months before (January 2002–June 2004) and 24 months after (January 2005–December 2006) the implementation of the admission screening policy; the implementation period (July–December 2004) was not considered in the analysis.

INT, implementation of the MRSA screening policy; slope before INT, monthly change before INT; change in level after INT, difference between first value after and last value before INT; change in slope after INT, monthly change after INT when compared with slope before INT; NS, not significant.

Model parameters for the incidence density of MRSA-infected patients: Durbin–Watson statistic (DWS) = 1.702 and determination coefficient ($R^2$) = 0.33. For nosocomial MRSA-infected patients, $DWS = 1.895$ and $R^2 = 0.32$, and for MRSA patients, $DWS = 1.764$ and $R^2 = 0.791$. 

Figure 2. Changes in the hospital-wide incidence density of MRSA-infected patients/1000 pd 30 months before and 24 months after the intervention (INT = implementation admission screening for MRSA, 6 month implementation period). All parameters in the full segmented regression model are significant, the slope (month-to-month change) before intervention is 0.007 MRSA-infected patients/1000 pd, the change in level is −0.163 MRSA-infected patients/1000 pd and the change in slope after intervention is −0.010 MRSA-infected patients/1000 pd (when compared with the slope before implementation of admission screening). This means that the slope after the 6 month implementation period is −0.003 MRSA-infected patients/1000 pd.
misclassification bias can be described by the proportion of nosocomial MRSA-infected patients of all cases of MRSA-infected patients (before intervention 55% and after 53% showing no relevant difference), with (and without) the assumption that MRSA infection in both time periods was observed independent of screening results.

Certainly, it was impossible to eliminate nosocomial MRSA infections during the course of the study. This is due to the fact that compliance with the established admission screening was not 100%, that indeed some cases of nosocomial MRSA infections occurred and that the admission screening was not established in the entire hospital. Therefore, additional screening cultures and the extension of the screening regime to further departments could lead to further improvement.

However, according to the ‘search and destroy’ policy, we saw the greatest success concerning the prevention of nosocomial MRSA infections in the early identification of MRSA carriers with subsequent decontamination of patients with elective surgical procedures.34

Moreover, infection prevention measures such as pre-emptive isolation of patients and patients at risk during microbiological testing could improve the infection control strategy. A rapid screening method such as PCR could likewise improve it. At our hospital, only conventional microbiological testing was performed, and no pre-emptive isolation of patients at risk is instituted. However, our infection control intervention succeeded in reducing nosocomial MRSA infections without any rapid screening test and pre-emptive isolation measures.

There are limitations of this study. First, active surveillance of drug prescriptions for the entire hospital does not exist at our hospital. Hence, a potential change in the antimicrobial therapy strategies would not be detected. For example, a limitation of fluoroquinolones use has been proven to decrease nosocomial MRSA infections by several studies and could be a confounder in our study.35,36

Lastly, neither did we conduct a systematic audit of compliance with subsequent isolation measures nor an evaluation of compliance with hand-hygiene procedures. However, on weekdays, our infection control nurses evaluated nearly every MRSA case patient with regard to the use of infection control measures. Thus, only short-time hospitalized patients were not evaluated for subsequent isolation measures. Furthermore, the prolongation of the observation period and the time-series analysis limit confounding to those factors changing at or around the same time as the intervention and are related to the outcome.

Conclusions

In conclusion, we have found that routine MRSA admission surveillance cultures, targeted to wards such as surgical wards and ICUs housing the largest number of MRSA risk patients, resulted in a sustained hospital-wide reduction in nosocomial MRSA infections.
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Acknowledgements

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Transparency declarations

No conflicts of interest to declare.

I. F. C. investigated the surveillance method, performed the data collection and the data analysis and wrote the manuscript. F. S. performed the statistical analyses. S. Z. supervised the microbiological diagnostic for MRSA and performed a part of the database analysis. S. S. initiated the admission MRSA screening and revised the manuscript. P. G. initiated the surveillance of MRSA and the admission screening and reviewed the manuscript.

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