Artificial Liver Support
Potential to Retard Regeneration?

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Hypothesis: The concept of an “artificial liver” has been in development for over 40 years. Such devices aim to temporarily assume metabolic and excretory functions of the liver, with removal of potentially hepatotoxic substances, thereby clinically stabilizing patients and preventing deterioration while awaiting transplantation. If sufficient numbers of viable hepatocytes remain, regeneration and subsequent recovery of innate liver function may occur. However, these devices have not yet become part of routine clinical use. Much less is known regarding the effect such devices have, if any, on circulating cytokines and growth factors and the subsequent effects on the regenerating liver. If these devices remove or reduce factors known to promote regeneration, is the rate of regeneration retarded? Conversely, does the incorporation of hepatocytes into bioartificial support systems confer an advantage through the production of growth-promoting factors from these cultured hepatocytes?

Data Sources, Extraction, and Study Selection:
Data were obtained using PubMed search for reports involving liver support, extracorporeal circuits, dialysis, growth factors, and cytokines. Those reports specifically looking at the effect of artificial liver support on cytokines and growth factors are discussed.

Conclusions: There is a paucity of information on the key events and substances involved in hepatic regeneration. In addition, there is a potential impact of liver support devices on the regeneration of substances associated with hepatic regeneration. Further study is needed.

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edema, but the exact processes leading to this are not yet clear.

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This review summarizes what is known of the key events and substances involved in hepatic regeneration and examines the potential impact of liver support devices on regeneration and substances associated with it.

MECHANISMS OF LIVER REGENERATION

Cells

Under physiologic conditions, hepatocytes are in the resting (G0) phase with low proliferative activity. However, after resection, most hepatocytes will undergo at least 1 round of replication before returning to a resting state. This process is stimulated by a highly controlled, complex, and incompletely understood sequence of events. The liver is a unique organ, as regeneration does not require the presence of progenitor stem cells, although they play an as-yet ill-understood role. Instead, proliferation of all mature hepatic cell types occurs, including hepatocytes, biliary epithelial cells, endothelial cells, Kupffer cells, andstellate cells.4

Hepatic oval cells are pluripotential progenitor cells capable of differentiation into hepatocytes, bile duct epithelia, intestinal epithelia, and possibly exocrine pancreas. The theory that these cells originate from within the biliary system is supported by their phenotypic similarity to bile duct epithelia, their expansion from the peribronchial area into the mesenchyme, and the reduction in numbers seen with selective damage to the peribronchial zones.3 However, some evidence suggests a bone marrow origin for some oval cells.6 Although their exact role is incompletely understood, the liver may regenerate by using oval cells in circumstances where large numbers of hepatocytes are damaged or hepatocyte replication is suppressed by hepatotoxins.7 Oval cells have receptors for hepatocyte growth factor (HGF), epidermal growth factor (EGF), and transforming growth factor α (TGF-α),8 and it has been shown that HGF promotes hepatocyte differentiation in bone marrow stem cells and oval cells.4 However, the mechanism of oval-cell activation, recruitment, and differentiation has not been fully elucidated, and further work is needed to clarify their role.7

Proliferation

In the regenerating liver, hepatocytes require a priming phase in which the hepatocyte undergoes a series of changes to enter into the cell cycle and become receptive to the actions of growth factors. This is supported by evidence that infusion of HGF, EGF, or tumor necrosis factor α (TNF-α) in rats caused replication in only 10% of hepatocytes; however, this figure increased substantially when these substances were infused into rats undergoing 30% hepatectomy, which suggests that a priming stimulation occurred at hepatectomy.9 Substances that initiate priming include TNF-α and interleukin 6 (IL-6), and it is during this stage that early genes are induced.10 These genes cover many different classes, including transcription factors, metabolic enzymes, inflammatory responses, and responses involved in cytoskeletal and extracellular matrix modification.11

The molecular mechanisms of regeneration have perhaps been most extensively investigated in the two-thirds hepatectomy of the rat model, which was described in 1931.12 In this model, DNA synthesis begins 12 to 16 hours after hepatectomy, peaking at 24 to 48 hours. Hepatocyte mitosis follows 6 to 8 hours later, with near restoration of volume at 3 days.13 Proliferation of bile duct epithelium peaks at 48 hours, Kupffer and stellate cells at 72 hours, and sinusoidal endothelial cells at 96 hours.14 Once the liver has reached optimal size, hepatocytes return to a quiescent G0 phase.

The rate of mitotic activity after liver resection, based on indirect measurements, is greatest 4 to 5 days postoperatively.13 In humans, two thirds of liver regeneration occurs within 2 weeks after major hepatectomy.16 Final regenerative volume ranges from 74%18 to 100% at 1 year after resection.17 Normal livers regenerate twice as fast as cirrhotic livers with comparable resection volumes.18,19

After resection, regenerating hepatocytes are initially arranged in nonvascularized clusters. Once hepatocyte proliferation has ceased, stellate cells move into the clusters and neovascularization occurs. Normal histological structure is seen 8 to 10 days after surgery.20 The modulation of extracellular matrix, collagen, matrix metalloproteinases, and tissue inhibitors of metalloproteinases during liver regeneration may help initiate and terminate the progression of quiescent hepatocytes into the cell cycle.21

Regulatory Substance

The process of liver regeneration requires a combination of cytokines and growth factors. Evidence of the role of circulating growth hormones arises from studies showing that after partial hepatectomy of the host animal, hepatic tissue transplanted into extrahepatic sites also undergoes DNA synthesis and replication.22 We characterize EGF, TGF-α, and HGF as complete mitogens, ie, each is capable of stimulating hepatocyte DNA synthesis in culture independently. Comitogens such as insulin, glucagon, epinephrine, and norepinephrine potentiate the action of mitogens, but are unable to stimulate DNA synthesis alone.23,24 (Figure 1).

Epidermal growth factor is a complete mitogen. In rats, sialoadenectomy (and the subsequent reduction in circulating EGF levels) reduces the regenerative response to that of rats undergoing partial hepatectomy, an effect that is reversed after administration of EGF.25 Exogenous EGF can stimulate regeneration in partially hepatectomized rats,26 but in cirrhotic rats it may need to be combined with insulin to increase the rate of DNA
carcinogenesis. When TGF-α exists in humans in 3 isoforms (TGF-α1, TGF-α2, and TGF-α3) and has a relative molecular mass of 25,000. It has a molecular structure of 112 amino acids, with 80% homology among the 3 isoforms, and is highly conserved between mammalian species. Its biological role is diverse, and disturbances in its production or downstream intracellular signaling have been implicated in several diseases such as atherosclerosis, fibrotic diseases, and cancer.

Transforming growth factor β exists in cellular proliferation, differentiation, apoptosis, angiogenesis, and tissue repair. Levels are elevated in hepatic fibrosis, and competitive blockade of the TGF-β receptors can prevent or reverse this process. Within the liver, TGF-β1 messenger RNA is found mainly in sinusoidal endothelium and Kupffer cells, with a lesser amount of TGF-β2 and TGF-β3. Stellate cells have little TGF-β, and hepatocytes express virtually no TGF in the resting state. After partial hepatectomy, TGF-β levels (mainly TGF-β2) increase in all cell types, but increased levels in stellate cells are seen only after bile duct injury.

After partial hepatectomy in rats, levels of TGF-β2 and TGF-β3 rise early, and TGF-β1 levels increase after 12 hours and peak at 20 hours, coinciding with decreasing hepatocyte proliferation. Infusion of TGF-β at the time of liver resection has been shown to decrease but not stop hepatocyte proliferation (although dose-response curves were not assessed), while increasing synthesis and deposition of extracellular matrix proteins. Delayed regeneration is seen in transgenic mice that over-express TGF-β.

However, the postresection increase of levels of TGF-β in the liver, with a peak at 48 hours, creates a paradox of hepatocyte proliferation in the face of elevated TGF-β levels. This anomaly may be explained by the finding that after liver injury by carbon tetrachloride, receptors for TGF-β1 on hepatocytes are downregulated for 72 hours. Recovery of expression after this time enables signal transduction to the nucleus and may have a role in terminating hepatocyte proliferation. Receptor down-regulation is not seen in hepatic stellate cells, enabling the production of extracellular matrix proteins around the proliferating hepatocytes.

Interleukin 6, with a molecular weight of 21 kDa, activates multiple signaling pathways that culminate in the induction of genes involved in growth and liver me-

Figure 1. Outline of action and interactions between mitogenic substances involved in hepatocyte proliferation. TNF-α indicates tumor necrosis factor α; IL-6, interleukin 6; u-Pa, urokinase-type plasminogen activator; HGF, hepatocyte growth factor; TGF, transforming growth factor; EGF, epidermal growth factor; +, positive effect on regeneration; and –, negative effect on regeneration.

Figure 2. Schematic representation correlating change in growth factors and cytokines after partial hepatectomy in rats with hepatocyte proliferation. HGF indicates hepatocyte growth factor; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; and TGF, transforming growth factor.
tabolism. After liver resection, levels of IL-6 and TNF-α are raised within the first few minutes and peak at 24 hours. Both of these substances are important in the initiation of regeneration and hepatocyte priming. In IL-6-deficient mice, hepatic DNA synthesis is significantly reduced, although recovery of normal liver weight is eventually achieved. Such mice have a 15% reduction in the number of hepatocytes that undergo DNA synthesis after partial hepatectomy. Administration of IL-6 before liver resection in these mice restores hepatocyte regenerative capacity. Tumor necrosis factor α receptor knockout mice show a similarly reduced regenerative response after hepatectomy, but also have reduced levels of IL-6. Again, this effect can be restored after injections of IL-6. These studies suggest that IL-6 release is initiated by TNF-α.

Hepatocyte growth factor is found in extracellular matrix of the liver, spleen, and kidney and bound to heparan sulfate, thrombospondin, and collagen types I, III, IV, V, and VI. It is a potent mitogen and causes proliferation in cultured hepatocytes in the absence of any other growth factors or cytokines. Homozygous gene deletions are associated with embryonic fatality partly due to arrested hepatic growth. In rats after liver resection, levels of HGF are elevated within 1 hour and remain elevated for 72 hours. Infusion of HGF in normal rats causes an increase in hepatocyte proliferation, but when preceded by a collagenase infusion, the rate of DNA synthesis is increased, implying that degradation of matrix is an important early part of regeneration.

Activated urokinase-type plasminogen activator is present in the liver within 1 minute of partial hepatectomy. Urokinase-type plasminogen activator activates HGF from inactive single-chain form to the biologically active 2-chain form. It also acts as a proteolytic enzyme to convert plasminogen to plasmin, thus contributing to the breakdown of extracellular matrix, which may prime hepatocytes for replication and release sequestered growth factors.

After liver resection, levels of norepinephrine are elevated within 1 hour. This elevation may help stimulate production of EGF from the Brunner gland in the duodenum and enhance the effects of EGF and HGF via adrenergic receptors. This elevation also may be involved in the early phase of DNA synthesis and has been suggested to have a role in resistance to TGF-β.

As described previously, administration of insulin in combination with EGF enhances regeneration in cirrhotic rat livers. Although insulin is not directly mitogenic, the diversion of insulin from the pancreas by portocaval shunt results in liver atrophy that can be corrected by means of exogenous insulin administration.

IMPACT OF LIVER SUPPORT DEVICES ON REGENERATION

The aim of a liver support device is to temporarily assume the detoxification and metabolic functions of the liver while awaiting regeneration of the remaining functioning hepatocytes and subsequent recovery of hepatic function. Such devices can be broadly separated into those that incorporate hepatocytes (biological) and those that have no cellular component (nonbiological). Nonbiological devices remove circulating toxins by means of filtration or adsorption using charcoal columns or albumin dialysis. Biological devices incorporate cultured hepatocytes within a bioreactor through which the blood or the plasma of the patient is perfused. Biological devices aim to not only remove circulating toxins but also replace the metabolic and synthetic functions of the liver.

The effects of liver support devices on liver function and survival, both clinically and in animal models, are reviewed elsewhere and therefore not considered as part of this review.

The effect of liver support on circulating cytokines and growth hormones remains to be elucidated. Do support devices remove or sequester these substances? If so, does this affect outcomes or regenerative rates? Do these devices affect complementary systems that may result in hemodynamic instability? Also, do biological support devices confer an advantage to regeneration through the production and secretion of mitogenic factors by the incorporated hepatocytes that may assist regeneration of the host liver? Is there a role for these devices in the removal of inhibitory factors, eg, TGF-β? To address this question, it is necessary to look at evidence from trials with liver support devices, as well as those with other extracorporeal systems such as renal dialysis.

Hemodialysis, Hemofiltration, Plasma Exchange, and Extracorporeal Circuits

Plasma exchange, where plasma is removed by means of plasmapheresis and replaced by donor plasma, has been used in patients with fulminant hepatic failure and has shown improvements in hemodynamic stability and cerebral function. However, this method may have serious adverse effects such as toxic effects, infections, and pulmonary or neurological complications.

For patients with acute liver failure, plasma exchange has variably been shown to reduce levels of TNF-α and IL-6 or to make no difference to levels unless combined with continuous hemodiafiltration.

Dialysis membranes may be made from natural materials such as cellulose or synthetic materials such as polysulfone, polymethylmethacrylate, or polyacrylonitrile with filtration of molecules with molecular weight of up to 40 kDa. Synthetic materials tend to be more biocompatible than the older cellulose-based membranes (ie, reduced production of proinflammatory cytokines and complement activation).

It is known that dialysis circuits induce a range of biological reactions. Levels of IL-6, TNF-α, IL-1, leucokriene, and superoxide become elevated, complement cascade is activated with increased levels of C3a/C5a; and endogenous pyrogens are elaborated from monocytes. Some of these, eg, TNF-α and IL-1, may be raised to sufficient levels to cause systemic effects, especially in septic or unstable patients. Levels of complement activation and production of pyrogens may be reduced with the synthetic membranes. In cardiopulmonary bypass circuits, similar activation of complement with elevated levels of the proinflammatory cytokines TNF-α, IL-6, and IL-8 is seen.

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Acute-phase proteins (e.g., α1-acid glycoprotein) are produced mainly by the liver and are regulated by proinflammatory cytokines. They are found in increased quantities in end-stage renal failure. Studies have compared the effect of adding the ultrafiltrate produced by high- and low-flux dialysis membranes to cultured hepatocytes. This showed that the ultrafiltrate causes reduced metabolic activity [by results of the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide MTT test] and increased cytotoxicity as measured by lactate dehydrogenase release in hepatocytes. The ultrafiltrates can also stimulate increased α1-acid glycoprotein release from hepatocytes, an effect more pronounced with high-flux compared with low-flux membranes. This finding suggests that dialysis can remove hepatotoxic substances, which may be an important factor in liver support systems incorporating it.

Dialysis membranes (polyacrylonitrile membranes more so than polysulfone membranes) may adsorb TNF-α, with minimal amounts removed by filtration owing to its large molecular weight (50 kDa). Interleukin 6 and IL-8 may be filtered to some extent, but removal has been postulated to be mainly by adsorption. However, little evidence exists of the effects of dialysis on other mitogenic substances such as HGF or EGF.

In septic patients with systemic inflammatory response syndrome or multiorgan dysfunction syndrome, in whom levels of circulating cytokines are known to be elevated, continuous hemofiltration can reduce IL-6 and IL-8 levels. Reduction of these cytokine levels is associated with improved urine output, blood pressure, and systemic vascular resistance, with decreasing dependence on inotropic support in this group of patients. However, these reductions have not been universally reproduced, and the role of hemofiltration in sepsis and its effect on survival have yet to be clarified by randomized controlled trials. Some evidence suggests that the fraction of inflammatory mediators removed by hemofiltration is insubstantial compared with that removed by endogenous clearance.

**Bioartificial Liver Support Devices**

To develop a bioartificial liver (BAL), a source of viable, functioning hepatocytes is required. At present, the predominant sources are human and porcine-derived cells. Primary human cells are a scant resource, as most suitable donor organs are required for transplantation programs. Human hepatocytes are difficult to replicate in vitro, and daughter cells have not been shown to express sufficient levels of liver-specific functions. Hepatocyte cultures derived from human hepatoblastoma cell lines have been used in liver support devices, but have lower levels of ammonia removal and amino acid metabolism compared with porcine hepatocytes. A concern with the use of hepatoblastoma and immortalized hepatocytes is the risk for transmission of potentially tumorigenic cells; therefore, interest has developed in the incorporation of "suicide genes." Although porcine hepatocytes are easily available, with a large yield per animal, concern still exists regarding immunogenic complications and potential transfer of porcine endogenous retroviruses. However, the future hepatocyte source may arise from the emerging field of hepatocyte stem cell research.

Techniques of hepatocyte culture and maintenance of viability and function are continually evolving. Difficulties arise in the balance between maintaining viability and subsequent loss of function. Once established, cell lines may quickly lose liver-specific functions. To address this issue, hepatocyte cellular morphologic features, bioreactor design, type of cellular scaffold, and culture medium have all been manipulated, with viable hepatocytes maintained in studies from 3 weeks to 5 months. Techniques of measuring viability include oxygen consumption, albumin secretion, lidocaine metabolism, ammonia removal, and urea synthesis. Although synthetic function can be measured by albumin secretion, evidence that cultured hepatocytes produce or are able to produce growth factors and cytokines is lacking. This may be difficult to answer experimentally, as cultured hepatocytes within bioreactors are not exposed to the stimulators of regeneration that are produced in hepatic failure. In addition, several of the substances involved in regeneration are secreted from surrounding hepatic stellate cells, which are not currently included within hepatocyte-incorporating bioreactors, but may be significant in studies using whole-organ liver perfusion as a liver support.

In rats that have undergone partial hepatectomy followed by partial devascularization of the remnant, the use of a BAL containing microcarrier-attached hepatocytes compared with sham liver-support devices (extracorporeal circuit without hepatocytes) has shown improvement in prothrombin time and reduced alkaline phosphatase, urea, and uric acid levels. However, no difference in serum levels of HGF between rats receiving BALs and those undergoing sham operation was found, with elevated levels seen in both groups. Levels of HGF RNA were also increased in the rats with a BAL but undetectable in the sham-operation rats. Decreased levels of TGF-β1 were found in rats treated with BAL support.

In humans with acute liver failure, both HGF and TGF-β1 levels are known to be elevated. In patients treated with an extracorporeal liver-assist device (ELAD) incorporating human C3a liver tumor cells within hollow fiber filters, levels of HGF were found to be elevated after 6 hours of hemoperfusion compared with untreated patients, then decreased back to the levels of the untreated patients after 48 hours. There was no change observed in plasma TGF-β1 level between the 2 groups. This observed elevation of HGF levels may be due to the heparin-binding qualities of HGF, thereby reducing metabolism and excretion by the remaining liver, as elevation of HGF levels is also seen in patients treated with continuous venovenous hemodialysis.

Another study using ELAD for patients with acute liver failure found that levels of TNF-α and IL-6 were elevated in all patients before treatment. Six hours after commencement of ELAD treatment, levels of TNF-α and IL-6 were further increased when compared with controls, but then decreased toward baseline within 48 hours. A small elevation seen in C-reactive protein levels may reflect the damaged liver’s inability to mount an acute phase re-
response to elevated cytokine levels. The level of anti-thrombin III (a marker of coagulation system activation) was elevated in all patients and had a small but not statistically significant rise after treatment with ELAD.73 None of these cytokine changes had hemodynamic effects on the patients.

Levels of TNF-α in hepatectomized pigs74 were found to be elevated when the animals were placed on an extracorporeal circuit containing hepatocytes compared with when they were perfused with an extracorporeal circuit alone, indicating that the presence of hepatocytes may cause activation of leukocytes and release of TNF-α.

Adsorption Columns/Albumin Dialysis

Although evidence suggests that the dialysis membrane itself may remove TNF-α by adsorption of molecules to the membrane, rather than through filtration or sieving,75 techniques using adsorptive columns may increase removal rates.

Hemoperfusion with albumin-rich dialysate has been shown to reduce circulating levels of IL-6 and TNF-α in addition to other substances with a high albumin affinity such as bilirubin, bile acids, benzodiazepines, middle chain fatty acids, and arachidonic acids76 in patients with acute liver failure. This system uses an albumin-impregnated hollow-fiber dialysis membrane with high-albumin dialysate. The albumin removes protein-bound substances into the dialysate, which is then cleaned by means of charcoal and resin adsorption columns, and the dialysate is recycled. This reduction of IL-6 and TNF-α levels is enhanced with albumin dialysis compared with hemodiafiltration with isotonic sodium chloride dialysate.77

The BioLogic-DT system (HemoCleanse, Lafayette, Ind) uses a parallel-plate cellulose membrane dialyzing against powdered charcoal to increase surface area. The system has been found to cause elevations in levels of TNF-α in patients with acute severe alcoholic hepatitis.78

Reductions in TNF-α and IL-6 levels have also been found in patients with systemic inflammatory response syndrome and organ failure undergoing a single treatment with powdered charcoal and silica.79 Initial use of sorbents such as charcoal and ion exchangers that allowed direct contact between blood and the adsorption column caused drops in fibrinogen levels and activation of the complement cascade.76 Therefore, systems now require either coated charcoal, which reduces adsorptive efficacy, or a plasma separation step.

COMMENT

The process of regeneration is incompletely understood, incorporating a complex interplay among numerous factors. Although some factors (e.g., HGF) are more potent stimulators of regeneration than others, it is clear that no one substance is singularly responsible for controlling this process. The evolving role of liver-support devices is, as yet, incompletely established and has yet to drive major inroads into routine clinical practice. The relationship between these devices and growth factors and its subsequent impact on regeneration remains to be fully elucidated. Some evidence suggests that elevations in levels of HGF, IL-6, and TNF-α occur in patients with acute liver failure treated with BAL support, but conflicting changes occur in IL-6 and TNF-α levels for those treated with nonbiological adsorption-based devices. Levels of TGF-β are unchanged in humans treated with BAL support, but levels of TGF-β in rats may be reduced.

The significance of these findings, if any, is unclear. Studies of the effects of liver-support devices and growth factors are limited and do not address the issue of the impact of these devices on regeneration. Although we know that reductions in IL-6 and TNF-α levels do not prevent regeneration, the fact the levels of these substances are affected suggests that levels of other cytokines, eg, HGF and EGF, will also be affected. Future studies of liver support devices need to incorporate evaluation of the effects of the device not only on liver function and survival but also on the rate of regeneration. Computed tomographic volumetric scanning or indirect measurements of DNA synthesis such as serum thymidine kinase levels may assess rates of regeneration. If liver support retards rates of regeneration, would there be a proportional increase in the number of oval cells seen in regenerating livers?

Comparison between the different causes of hepatic failure and liver-support devices may show differing effects on growth factors and regeneration. This may be a reflection on the differing pathogenesis of liver failure between acetaminophen-induced failure and autoimmune causes, for example.

If liver support devices are shown to retard rates of regeneration, then the period of use required in patients may be longer than expected. However, if promotion of regeneration is demonstrated, then the potential implications for earlier use in an extended group of patients with hepatic failure may be a possibility.

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Prevalence and Risk Factors for Carriage of Methicillin-Resistant Staphylococcus aureus at Admission to the Intensive Care Unit: Results of a Multicenter Study

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Background: Detection of methicillin-resistant Staphylococcus aureus (MRSA) carriers on admission to the intensive care unit (ICU) is an important component of strategies for controlling the spread of MRSA.

Methods: A prospective multicenter study was conducted in 14 French ICUs for 6 months. All patients were screened within 24 hours after admission, using nasal and cutaneous swabs. In addition, clinical samples were obtained. Patient data collected on ICU admission included presence of immunosuppression; history of hospital stay, surgery, antimicrobial treatments, or previous colonization with MRSA; chronic health evaluation and McCabe scores; reason for admission; whether the patient was transferred from another ward; severity of illness; presence of skin lesions; and invasive procedures. Risk factors for MRSA carriage at ICU admission were estimated, and significantly associated variables were used to develop a predictive score for MRSA carriage. A cost-benefit analysis was then performed.

Results: Of the 2347 admissions with MRSA screening, 162 (6.9%; range, 3.7%-20.0% among ICUs) were positive for MRSA, of whom 54.3% were detected through screening specimens only. Of the 2310 first admissions (vs repeat admissions) to the ICU, 96 were newly identified MRSA carriers. Factors associated with MRSA carriage in the multivariate analysis were age older than 60 years, prolonged hospital stay in transferred patients, history of hospitalization or surgery, and presence of open skin lesions in directly admitted patients. Only universal screening detected MRSA carriage with acceptable sensitivity. A cost-benefit analysis confirmed that universal screening and preventive isolation were beneficial.

Conclusions: The prevalence of MRSA carriage on admission to the ICU is high in this endemic setting. Screening for MRSA on admission is useful to identify the imported cases and should be performed in all ICU-admitted patients. (2003;163:181-188)

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