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The state of the science

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This review was derived from the first Association for Professionals in Infection Control and Epidemiology (APIC) "State of the Science" lecture, which was delivered at the 30th Annual APIC Educational Conference and International Meeting in San Antonio, Texas, in June 2003. It begins with a few comments about science in general and then moves on to comments about the current state of the science in question, the epidemiology and prevention of adverse events associated with health care. It focuses on the topic that has been both the traditional and the continuing predominant focus of health care epidemiology, health care-associated infections. Of the hundreds of recent publications in this field, many were very good. In the space allotted, however, the review will necessarily cover only selected topics that will hopefully provide some insight into the current state of the science.

GENERAL COMMENTS ABOUT SCIENCE

Science has been defined by *Webster's Dictionary* as "systematized knowledge derived from observation, study, and experimentation carried on to determine the nature or principles of what is being studied." At a recent Festschrift honoring the career of my scientific mentor, Dr Jack Gwaltney, Jack's mentor Dr Bill Jordan commented on the effects of chance on science and on scientific careers. Many are aware that a *Penicillium* spore landed by chance on an agar plate seeded with *Staphylococcus aureus* by Alexander Fleming and that this led to his discovery of penicillin and the dawn of the antibiotic era. Many like to emphasize the serendipity of this finding, but Fleming had been working for years searching for anything that would inhibit *S aureus* like that, illustrating Pasteur's statement that "chance favors the prepared mind."

It has been said that science is like a mosaic, with each bit coming from an individual study. By looking at the pattern of how all the studies come together, one can see when the bulk of the evidence supports a particular hypothesis as opposed to another. I like this simile because it emphasizes the importance and interdependence of all studies, including those in the past, not unlike Newton's statement "If I have seen further than others, it is by standing upon the shoulders of giants."

Occasionally there is a major paradigm shift, however, that suddenly allows a much larger change in the mosaic. It does not necessarily negate all the data previously collected but may change the interpretation of the whole pattern. For example, Howard Margolis,¹ a professor of the history of science at the University of Chicago, believes that the explorations of Columbus and others resulting in the publication of a New World map in 1507, which showed the New World on the back side of the earth, may have resulted in Copernicus, an astronomer who studied both medicine and law as a young man, being able to take data commonly available for centuries and draw radically new conclusions. In 1543, Copernicus published his book about the solar system, *De Revolutionibus*, in which he said that earth was not the center of the universe but merely a planet among planets, rotating around the sun. He began the book with an apology for presenting an idea that he knew would seem absurd. He ended the book by warning philosophers and theologians not to meddle in this lest they make fools of themselves.

Margolis¹ says that the heliocentric hypothesis was an idea whose time had come, which turned the world of science inside out and seemed to catalyze rapid progress in science. He notes that there were major scientific accomplishments at the dawn of what some have called the scientific revolution at the beginning of the 17th century, the likes of which had not been seen in the previous 14 centuries. He also claims that all the very important discoveries were made by a small number of Copernicans, men like Galileo who embraced and were apparently inspired by what Copernicus had done. Margolis says that although Copernicans were still vastly outnumbered at this time, "they could see that the opposition was in retreat and making a last stand in a bastion that looked ridiculous to Copernicans."

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Table 1. Some scientists who have advocated a scientific conclusion they believed to be true before it was widely accepted by the scientific community

Copernicus
Edward Jenner
Pierre Charles Alexander Louis
Charles Darwin
Louis Pasteur
John Snow
Joseph Lister
Ignaz Philip Semmelweis
Florence Nightingale
Oliver Wendell Holmes
Barry Marshall (<i>H pylori</i> and ulcers)

Some have expressed concern that scientists like Copernicus sometimes “go out on a limb” and advocate a scientific conclusion they know to be true before it is widely accepted by the scientific community, arguing that scientists should be dispassionate and that dispassionate scientists shouldn’t care whether a scientific idea is accepted or not. In an article on “the social imperatives of medical research,” however, Eisenberg² observed that “not to act is to act.” Table 1 shows that the history of science has, in fact, been filled with scientists advocating scientific findings that they found to be true before the scientific community was comfortable with their conclusions. Moreover, history shows that other scientists vigorously opposed these new hypotheses. For example, when Paul Lauterbur, the 2003 Nobel laureate in medicine, first published an article on magnetic resonance imaging, he said he was advised by previous Nobel laureates that magnetic resonance imaging would never work. Most of the names listed in Table 1 are probably as well-known as the hypotheses the scientists advocated. A possible exception is Barry Marshall, a recently active scientist who joined the faculty at the University of Virginia a couple of decades ago. He was derided for years for believing something that most specialists in the area considered to be absurd, that a bacterial infection could cause peptic ulcers. I added him to the list because virtually all now recognize that he was right.

One of the Copernican-like paradigm shifts in medical science involved Pierre Charles Alexander Louis, who has been credited as being a father of epidemiology for introducing what he referred to as *la méthode numérique* (ie, the numerical method), which was essentially the use of biostatistics for making clinical epidemiologic decisions in the 1820s. Using this method, Louis found that the time-honored practice of bloodletting, which was known to have been used for at least 24 centuries (since the time of

Table 2. Maternal mortality rates Allgemeines Krankenhaus, Vienna³

	Ward 1	Ward 2
1846	11.4%	2.7%
1847	Calcium hypochlorite washings begun	
1848	1.3%	1.3%

Hippocrates), didn’t work. His publication was met with controversy and dismay. It took decades for his work to be accepted as correct and the practice of bloodletting to be abandoned. Louis had many students from both Europe and America, including Oliver Wendell Holmes. Josef Skoda studied under Louis and then taught Semmelweis at the University of Vienna. Louis’s numerical method is displayed in Semmelweis’s³ most famous study (Table 2), which also required decades for acceptance by the medical community. Full acceptance and implementation of *la méthode numérique* took quite a few decades.

Inferential statistical comparison of rates, a step beyond anything imagined in Louis’s day, still hadn’t caught on by the middle of the 20th century. For example, when streptomycin became available in the 1940s, it was tried as monotherapy for patients with tuberculous meningitis, which had previously been universally fatal. The first small open trial using streptomycin showed a case fatality rate of only 50%. This was viewed as miraculous, and it became an accepted therapy with no discussion about or calculation of statistical significance. This was related to me by Dr Thomas Hunter,⁴ the physician who discovered the synergy between streptomycin and penicillin for treating streptococcal endocarditis in the 1940s.

GENERAL COMMENTS ABOUT THE SCIENCE OF HEALTH CARE EPIDEMIOLOGY

The first volume of *Infection Control* was published in 1980. Seventy-five percent of its original articles did not include a statistical methods section and did not compare rates with inferential statistics. In 1990, *Infection Control and Hospital Epidemiology* published 3.6-fold more articles, and a large majority of the original articles compared rates using inferential statistics. It is clear that the pace of acceptance of statistics in medical research increased rapidly during the 1980s, and not just in journals like *Infection Control and Hospital Epidemiology*, which are devoted to epidemiology.

A Medline search of the terms *nosocomial* or *cross infections* identified 29,080 publications since 1966, a mean of 765 per year. Publications in the 3 journals with a special focus on this area, *Infection Control and*

Table 3. Criteria for causal inference⁵

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1. Strength of association
 2. Consistency of evidence
 3. Temporal relationship
 4. Biological gradient
 5. Reversibility with experiment
 6. Specificity
 7. Coherence of evidence
 8. Reasoning by analogy
 9. Plausibility
-

Hospital Epidemiology, American Journal of Infection Control, and the *Journal of Hospital Infection*, have accounted for 26% of all publications with these Medical Subject Headings terms during these years. The most recent 60 articles with these Medical Subject Headings terms were published in 46 different medical journals. Those who think they are keeping up by reading just 1 infection control journal should perhaps think again.

The Medline search also found that 22 (0.076%) of the 29,080 publications using the terms *nosocomial* or *cross infections* since 1966 had also used the term *randomized controlled trial (RCT)*. None of these 22 studies were published in the 3 journals with a special focus in this area. Medline listed 20 other articles that used the term *randomized controlled trial* but did not use the terms *nosocomial* or *cross infections*, however, accounting for 0.27% of all publications in these 3 journals. For comparison, 2571 articles that used the term *randomized controlled trial* were identified among 1,754,019 English-language medical articles from 2000 through 2003 (ie, accounting for 0.15%).

RCTs are on average more expensive to undertake, so extramural funding would be helpful for conducting them. There has been political support for investigator-initiated grants dealing with infections, such as malaria or leishmaniasis, that occur predominantly or entirely in third world countries, but not for grants related to nosocomial infection (NI) in American hospitals. A counterexample has been the National Institutes of Health (NIH) support of a Mycosis Study Group for conducting a series of studies of therapy of various fungal infections, some of which were nosocomial. For this reason I wrote to the director of the National Institute of Allergy and Infectious Diseases a decade ago, proposing the creation of a Nosocomial Infections Study Group that would have a budget and could distribute public funds for undertaking studies hard to manage without such funding. The reply was that the Centers for Disease Control and Prevention (CDC) gets all monies related to that problem area, even though at the time there was no mechanism for individual investigators to submit a grant for extramural funding. This means that

funded RCTs for NIs have usually been smaller than might be optimal for statistical power considerations. It also means they have often involved funding by a corporation with a vested interest in the results and thereby may have been subject to the selection of investigators with a track record favorable to the company.

The Medline search also found that none of 61 publications on the terms *smallpox* and *vaccine* during 2003 and none of 685 articles on *severe acute respiratory syndrome (SARS)* published between March and June 2003 appeared in the 3 journals with a special focus on health care-associated infections.

Austin Bradford Hill⁵ proposed criteria for judging whether or not an association is causal (see Table 3). One of these, reversibility with an experiment, could obviously involve an RCT. Hill did not say that an RCT was always necessary, but would be preferable in certain situations, such as when clinicians were likely to choose the active drug for their most severely affected patients and allow those with milder illnesses to get the placebo (ie, creating a selection bias).

It has recently been suggested that the results of observational studies cannot be trusted because of frequent error.⁶ If true, the field of health care epidemiology is in serious trouble because, as just demonstrated, these studies have constituted the vast majority of studies in this field, as they have in most of medicine. Three recent meta-analyses compared the results of many RCTs and observational studies examining the same questions and found that the results were generally in agreement both qualitatively and quantitatively.⁷⁻⁹ For example, Fig 1 offers a graph from one of these studies showing the point estimates of RCTs and observational studies for several different questions. The authors, a well-known and respected epidemiology group from Yale University, concluded that the results of observational studies did not systematically overestimate or underestimate the effects of an intervention. They also noted that there was sometimes greater variation among the results of RCTs. Some RCTs showed obviously wrong results, if the mean results of all RCTs of the question are taken as mostly likely reflecting truth. This makes it clear that a single study of either type cannot be considered definitive and that consistent results from different studies by different investigators in different populations are needed, as emphasized by Hill. Each of the 3 meta-analyses concluded that randomized trials are the design of choice but found that the data from observational studies of the same question usually yielded comparable results.

One of the few areas within hospital epidemiology for which there have been multiple randomized trials has been the use of antiseptics for prevention of catheter-related infections. Use of chlorhexidine

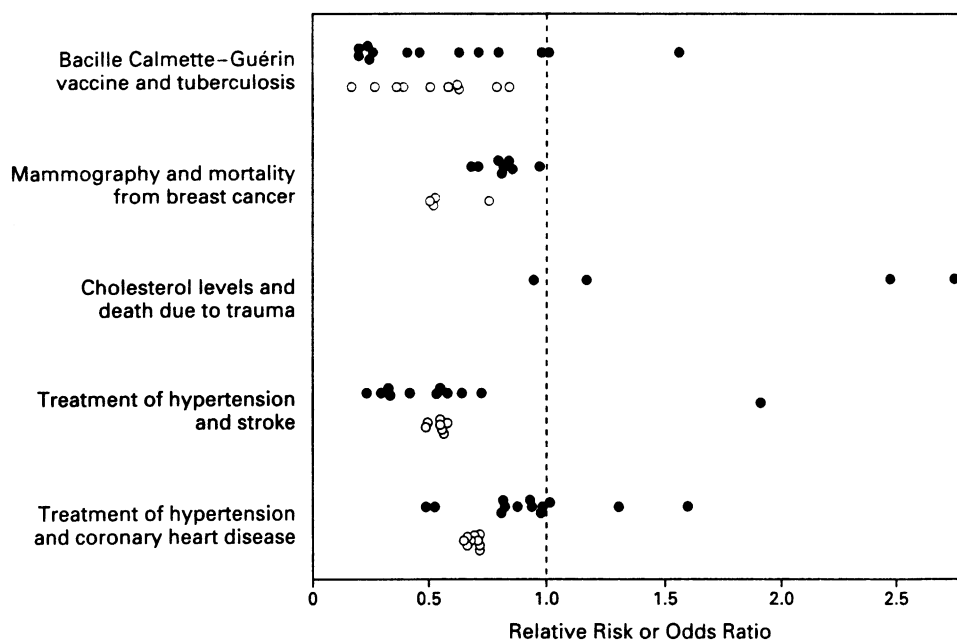


Fig 1. This graph shows the point estimates of RCTs in black and observational studies in open circles for several different questions. These data suggest that studies of the 2 types tended to give similar results and that RCTs of a particular question showed variable results for 4 of the 5 topics. Republished with permission from an article originally published in the *New England Journal of Medicine* by Concato.⁷

gluconate at the catheter site significantly decreased catheter colonization in 6 of 7 RCTs, as compared with use of povidone iodine or alcohol. Three of the 6 also found significant reductions in catheter-related bloodstream infection (BSI), whereas the other 3 had inadequate power to address this outcome.

Multiple randomized trials have also been done regarding scheduled replacement of central venous catheters (CVC). After an RCT of this question was started at my hospital, my coinvestigators and I submitted a grant for NIH funding to make the study larger than would be possible otherwise. Because there was no NIH section on hospital-acquired infections, the grant was forwarded to an anesthesiology section. The response was that the topic was not of great interest and that the study probably wouldn't be decisive. After the *New England Journal of Medicine* published the study, which found that scheduled replacement of CVCs did not prevent infection and actually harmed patients,¹⁰ it was calculated that stopping the practice would net US hospitals approximately \$500 million in collective savings per year simply by avoiding the costs of routine CVC replacement, without including excess costs because of complications engendered by routine CVC replacement. In 1996, CDC issued a new guideline regarding prevention of catheter infections and strongly recommended against scheduled replacement of CVCs, citing the University of Virginia study reporting that it did not work as category IA evidence.¹¹ None of

the studies showing that this worldwide practice didn't work were conducted by the CDC or with extramural support from CDC, illustrating the difficulty in getting answers to important questions regarding NIs.

A survey published in 1998 reported that 52% of surveyed intensive care units in Britain had continued using scheduled CVC replacement and that 59% of those using scheduled CVC replacement couldn't provide a reason for the practice.¹² This reveals another unfortunate part of the state of the science. My hospital changed its policy 14 years ago, but a recent survey of house staff found that 10% were using scheduled CVC replacement again (unpublished data, Hall KK and Farr BM). Inertia is a powerful force in physics, and tradition is powerful in human systems.

The authors of a recent IDSA/SHEA/SCCM guideline regarding management of catheter infections noted that almost none of the topics covered had been studied using RCTs.¹³ Likewise, a recent SHEA/IDSA/HICPAC/APIC guideline on hand hygiene strongly recommended alcohol handrubs for preventing NIs even though there had not yet been a single RCT of this question.¹⁴

A REVIEW OF HEALTH CARE EPIDEMIOLOGY ARTICLES FROM JUNE 2002 THROUGH JUNE 2003

A recent meta-analysis of RCTs of nutritional supplements reported dramatic reductions in overall

NIs, pneumonia, and bacteremia.¹⁵ This is notable because these studies have not generally been published in infection control journals. This suggests the need for careful scrutiny by health care epidemiologists and/or confirmatory studies.

SARS is likely the biggest news story in infectious diseases epidemiology during the past year, with notable articles showing a significant association with a novel coronavirus,¹⁶ that 77% of SARS cases in a Toronto epidemic involved NI of health care workers,¹⁷ and that infection control measures worked when used, especially wearing masks or respirators.¹⁸

A recent study in the *Annals of Internal Medicine* found that community-acquired BSI were now frequently health care-associated and that the mortality of such cases was similar to that of nosocomial BSI and higher than for other community-acquired BSI.¹⁹

Four studies in the *New England Journal of Medicine* were included in the review. The first reported that nurse staffing in general and RN staffing in particular were inversely correlated with risk for multiple adverse outcomes, including infections and deaths from infections (pneumonia or sepsis).²⁰ The second article reported that a manufacturer's recall of a bronchoscope with a defective part linked to ineffective disinfection led to recognition of a sizable outbreak of *Pseudomonas aeruginosa* infections and possibly 3 deaths in 1 hospital.²¹ The hospital's outbreak stopped with the recall. The third article described 1 of the 2 vancomycin-resistant *S aureus* cases reported in the United States during 2002.²² Pulsed field gel electrophoresis showed the patient's vancomycin-resistant *S aureus* to be identical to the methicillin-resistant *S aureus* (MRSA) of the patient and her friend. Polymerase chain reaction revealed *vanA*, which on sequencing was identical to the *vanA* in the patient's Vancomycin-resistant *Enterococcus* isolate and in transposon TN 1546. The minimal inhibitory concentration to vancomycin was 1,024 µg/mL, and the authors concluded that "this finding underscores the importance of extending efforts to prevent and reduce spread of MRSA." The fourth article reported the results of an RCT of prophylactic intranasal mupirocin to prevent postoperative *S aureus* infections.²³ It found no significant surgical-site infection (SSI) prevention, but power was only 75.6%; among *S aureus* carriers there was a strong trend toward SSI prevention, and overall postoperative *S aureus* infections were reduced significantly. Multiple prior RCTs of mupirocin prophylaxis have shown significant prevention of dialysis-related infections. There also have been multiple observational studies with both surgical and dialysis patients, suggesting significant prevention.

Three studies in *Clinical Infectious Diseases* were included in the review. The first found that wearing

gowns and gloves for care of VRE patients resulted in lower VRE rates than when gloves only were worn.²⁴ The second found that *S aureus* SSI were associated with a 2-fold higher risk of secondary BSI than occurred with all other etiologic agents.²⁵ The third study reported a significantly higher mortality rate for patients with MRSA infections with intermediate resistance to vancomycin (VISA), as compared with infections caused by MRSA fully susceptible to vancomycin.²⁶ This remained true in multivariate analysis after adjustment for other known predictors of hospital mortality.

An article from the *Archives of Internal Medicine* found that multiresistant clones of *Acinetobacter baumannii* and *P aeruginosa* were spreading throughout the 15 hospitals in Brooklyn, including some "resistant to all standard antibiotics."²⁷ A single clone accounted for 62% of the *A baumannii* isolates and was found in all 15 hospitals. Carbapenem resistance was associated with cephalosporin use at each of the hospitals. Ribotyping showed that 3 clones accounted for nearly half the multiresistant *P aeruginosa* isolates found in most hospitals. The authors concluded that more aggressive control measures were needed.

Six studies in the *Journal of Hospital Infection* were included in the review. The first reported that 2 clones of MRSA accounted for most bloodstream isolates of MRSA in 12 hospitals in 7 states stretching from New York to Georgia; 51% were clone A, 9% were closely related to clone A, and 20% were clone W.²⁸ Clone A infected patients in all 12 hospitals, accounting for 17% to 78% of MRSA bacteremias in the different hospitals. Clone W caused infections in 10 of the 12 hospitals. The second study reported that a selective mannitol broth offered a "convenient, inexpensive, sensitive method for high throughput screening for MRSA."²⁹ A third study reported rates of invasive aspergillosis in Paris hospitals.³⁰ There was no seasonal variation, and crude mortality was 63%. Incidence was 8% in patients with acute myelogenous leukemia, 6% with ALL, 13% after allogeneic stem cell transplant, 1% after autologous stem cell transplant, 11% after heart-lung transplant, and 0.4% after kidney transplant. The fourth study reported molecular typing of *Aspergillus fumigatus* isolates but reported inability to locate the environmental reservoir for patient infections despite finding many *A fumigatus* isolates from the environment.³¹ A fifth article examined risk and prognostic factors for candidemia.³² Catheter removal was associated with higher survival (71% vs. 47% when the catheter was not removed). Septic shock occurred in 17%. The sixth study reported a significant decrease in infection in an intensive care unit that continued for years after hiring a dedicated infection control professional for that unit. Infection rates were reduced by 42% over 3 years and 33% over 5 years.³³

Eight studies from the *American Journal of Infection Control* were included in the review. The first showed repeatedly that when surveillance cultures and contact precautions were implemented VRE rates fell significantly, and when they were withdrawn rates increased significantly.⁵⁴ This showed both reversibility and specificity for control with this approach, 2 of Bradford Hill's criteria for causality. Use of standard precautions was the control measure that did not work repeatedly for controlling VRE spread. The second article described an Italian study reporting a two thirds reduction in MRSA infections in a unit undergoing an MRSA epidemic after enteral vancomycin was used to suppress MRSA colonization.⁵⁵ Neither VRE nor VISA was isolated from surveillance or diagnostic samples.

A third study found that the earpieces of stethoscopes left in an isolation room often were contaminated with pathogens, leading the authors to suggest disinfection of such stethoscopes before use.⁵⁶ A fourth study reported a Delphi assessment of the number of infection control professionals needed per 100 beds; 32 panel members from 20 states participated in the iterative process, which concluded that 0.8 to 1.0 infection control professionals were needed for every 100 occupied acute care beds.⁵⁷ The fifth *American Journal of Infection Control* study reported rates of dialysis-associated infections from a national surveillance system.⁵⁸ Some centers had significantly higher than average rates, whereas others had significantly lower than average rates. Fistulas were associated with 0.56 infections per 100 patient-months, grafts with 1.36, cuffed catheters with 8.4, and noncuffed catheters with 12 per 100 patient-months. A sixth study reported the many ways that an alcohol dispenser might not work and suggested checking out a company's dispenser before buying its product.⁵⁹ The seventh study reported that although alcohol is kinder and gentler to hands, there can still be rare individuals with adverse reactions, sometimes allergic.⁴⁰ The eighth report dealt with an even rarer adverse effect of alcohol, fire, pointing out the need to be aware of what generates sparks of static electricity and to avoid doing what this health care worker did.⁴¹ The health care worker squirted alcohol into the palm, pulled off an isolation gown, and then touched the metal frame of a door, resulting in an apparent spark of static electricity that ignited the palm full of alcohol; the fire was extinguished without serious injury.

Eight studies published in *Infection Control and Hospital Epidemiology* were included in the review. The first reported that a polymerase chain reaction of nasal swabs could accurately detect *S aureus* preoperatively, allowing intranasal prophylaxis.⁴² The authors conducted a cost analysis and concluded that this represented an accurate, rapid, and cost-effective

method for detecting *S aureus* carriers for preoperative intervention. A second study showed that an intraoperative time alert from a computer resulted in a significantly higher rate of redosing when indicated, as recommended by national guidelines.⁴⁵ The third study reported 28 hepatitis B infections of patients from a hepatitis B-infected surgeon over a 4-year period.⁴⁴ The surgeon was found to have been carrying hepatitis B at a high level for at least a decade before transmissions began to be recognized. Of note, transmission occurred during both low- and high-risk surgical procedures. A fourth study summarized the documented cases of occupational HIV infection during the first 20 years of the HIV epidemic in the United States, including some despite postexposure prophylaxis.⁴⁵ A graph in the article showed that transmission to health care workers has been greatly reduced with current control measures. A fifth study suggested that mupirocin doesn't work to eradicate mupirocin-resistant MRSA.⁴⁶ The authors strongly suggested susceptibility testing. The sixth was another study finding that VRE rates were significantly reduced when both gowns and gloves were worn for care of VRE patients, as compared with when gloves only were worn.⁴⁷ This study also showed a significant decrease in clonal VRE spread. The seventh study showed a 38-fold higher frequency of nosocomial clonal spread of MRSA when patients were not detected by screening cultures and placed into contact precautions.⁴⁸ This suggests that standard precautions cannot be relied upon to control nosocomial MRSA spread even in a country like the Netherlands, with optimum antibiotic control and perhaps better overall compliance with hand hygiene.

The eighth article from *Infection Control and Hospital Epidemiology* was an evidence-based SHEA guideline for preventing nosocomial transmission of MRSA and VRE.⁴⁹ It recommends active surveillance cultures be used to identify colonized patients so that they can be cared for using contact precautions throughout the health care system. It cites more than 40 open trials showing control with this approach. It is posted on the position paper section of the SHEA Web site (www.shea-online.org), which non-SHEA members are welcome to access and print out free of charge. Related information on methods for culture, algorithms for deciding when to culture, and slides for educating health care workers are available at www.pppsite.org. As mentioned earlier, the SHEA guidelines cited more than 40 studies showing control of MRSA and VRE using active surveillance cultures and contact precautions, but 8 more studies showing control of MRSA or VRE with this approach were presented at the national SHEA meeting in Arlington in April 2003.⁵⁰⁻⁵⁷

Last but not least, another abstract presented at the national SHEA meeting reported a nosocomial

outbreak of MRSA infections caused by the new *mec IV* strain resistant only to penicillin and oxacillin that has been causing community spread in some areas.⁵⁸

CONCLUSION

More than 750 studies have been published annually in scores of medical journals regarding health care-related infections and have yielded much valuable information. The number has increased in recent years with the arrival of new issues such as smallpox vaccination of health care workers for bioterror preparedness and SARS and monkeypox outbreaks. Nevertheless, there remain significant challenges to the state of the science. Relatively few governmental sources exist for funding of independent, investigator-initiated grants for research regarding the epidemiology, prevention, or management of health care-related infections. As a result, most of aforementioned studies have been conducted on a shoestring budget, using the existing resources of individual hospitals. Many hospitals have recently reduced their support for infection control, and some weren't investing that much to start with. The APIC Research Foundation has traditionally funded very small grants (ie, of a size unlikely to definitively address any question). The CDC has recently advertised the creation of a new office that may someday soon begin accepting grants for conducting research on NIs. The NIH has recently expanded the Mycosis Study Group to include studies of bacterial infections, but has funded very few grants on this topic. The most important resource has been the people in this field who have done a great deal of work over the past 3 decades with very little financial support.

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