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Occult Nosocomial Infections

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ABSTRACT

Even with a good surveillance program, nosocomial infections may be not recognized because of several reasons: absence of symptoms or prolonged incubation period (eg, viral bloodborne infections, tuberculosis); problems with the microbiological diagnosis, because adequate specimens may be difficult to obtain or special methods should be used (eg, fungal infections, virus, new agents); shorter hospital stays (eg, surgical-site infections); difficulty in distinguishing between nosocomial and community-acquired infections (eg, influenza); and failure to detect clinically relevant colonization (eg, multiresistant microorganisms). Because of the important potential consequences of occult nosocomial infections, specific surveillance programs should be designed to address these problems (*Infect Control Hosp Epidemiol* 1998;19:593-596).

The exact incidence and burden of nosocomial infections are not known and are not likely ever to be so. The methods used for surveillance are the main determinants affecting the reliable detection of nosocomial infections. Even with extensive active and passive case-finding methods, some cases will remain undetected because of the very nature of the infection. Several possible reasons for this are summarized in Table 1.

LONG INCUBATION PERIOD, ASYMPTOMATIC INFECTIONS

Some infections may remain asymptomatic for a long period of time, if not forever. Even asymptomatic infections may have important consequences in terms of transmission.[1] Examples of pathogens responsible for this type of presentation are bloodborne viruses, such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus, mycobacteria, and prions.

For HBV, the incubation period varies from 4 to 28 weeks, and only 40% to 50% of patients will present with an icteric phase. Many of the hepatitis B surface antigen (HBsAg) carriers do not recall any symptomatic disease. Hepatitis C virus has an incubation of 20 to 90 days, and only 25% of cases will present with icteric hepatitis. Nowadays, these diseases presumably are rarely acquired nosocomially because of the systematic testing of blood transfusions and graft donors, and because of the use of standardized procedures for the disinfection of instruments or devices that may transmit the virus from patient to patient. However, this still may occur if these procedures are not followed, as illustrated recently by the transmission of HCV through inappropriately treated endoscopes.[2,3] It is easy to understand that such cases will be very difficult to recognize in the absence of clear circumstantial evidence and a careful epidemiological evaluation. Bloodborne agents also can be transmitted by carriers among healthcare workers (HCWs) performing invasive procedures. Several dozens of clusters of HBV infections linked to dentists or surgeons infected by HBV have been described. In 1992, the Centers for Disease Control and Prevention (CDC) investigated 33 such reports, which involved 9 dentists, 20 surgeons, and 4 other HCWs, responsible for a total of 330 cases. Most of these reports involved dentists and surgeons who were both HBsAg- and hepatitis B e antigen (HBeAg)-positive. The risk of transmission was estimated to be 0.06 per 100 procedures. In a recent report, four surgeons who were HBsAg-positive but HBeAg-negative were found to be responsible for 5 cases among 216 investigated patients.[4] With the widespread use of HBV vaccination of HCWs and with the introduction of universal childhood vaccination, this problem probably will become negligible in developed countries in the future. However, there still will be a very long transition phase during which the risk will persist because presently practicing surgeons and dentists may have contracted the infection before vaccination was imple-

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TABLE 1
OCCULT NOSOCOMIAL INFECTIONS

Causes	Examples
Asymptomatic disease	CMV, HBV, HCV
Long incubation period	HIV, HBV, HCV, mycobacteria, prions
Difficulty or lack of diagnosis	Fungi, some virus, new pathogens, *Legionella*
Short hospitalization stay	Surgical-site infections
Possible nosocomial transmission	*Pneumocystis carinii*
Difficulty in differentiating nosocomial from community-acquired infection	Influenza, rotavirus
Colonization	Multiresistant microorganisms

Abbreviations: CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

mented.

Hepatitis C virus also can be transmitted from HCWs to patients, but there are only a few reports.[5-7] The risk of transmission of HCV from patients to HCWs after percutaneous exposure appears to be similar to the risk of transmission from HBsAg-positive but HBeAg-negative source patients (2%-10%). Thus, the risk of transmission from HCWs to patients is probably low.

The risk of nosocomial transmission of HIV from HIV-infected HCWs to patients has been assessed extensively following a report of a dentist who had been implicated in the transmission of HIV to five of his patients.[6] Among 22,171 tested patients treated by 51 HIV-positive healthcare workers, 113 HIV-positive patients were found.[8] Twenty-eight were infected prior to the procedure. Most of the 85 remaining patients had established or potential risk factors. In 16 of the 23 cases without risk factors, cross-infection was excluded by sequencing of the HIV strains. Thus, although a few cases were not investigated completely, no case of transmission was documented. In another investigation of an HIV-positive surgeon in France, transmission was documented in 1 of 968 investigated patients (unpublished data, report to the French Health General Direction, December 1996). From these studies, it is concluded that the risk of transmission from HIV-infected HCWs to patients is very low.

Tuberculosis is another infection where nosocomial acquisition may be unnoticed or underestimated because of the long incubation period, which may preclude clear epidemiological links with the hospitalization, and because only 5% to 10% of infections eventually will lead to disease. Many published clusters or outbreaks show that cases often are discovered only after an extensive investigation. Often, months may have elapsed before the outbreak is recognized, sometimes involving many patients whose links are established only retrospectively.[9-11] Detection of such clusters for outbreaks may be complicated by the fact that patients may be rehospitalized in different hospitals.[12] Moreover, the exposure to the infectious patient may occur during a very brief encounter, such as staying in the same outpatient room, an event that may not be traced.[13] Nosocomial acquisition of tuberculosis among HCWs also can be underestimated seriously unless a good and systematic tuberculin testing program is in place. The main component of prevention of tuberculosis is early detection and treatment of cases, adequate ventilation of hospital areas where tuberculosis patients may stay and respiratory isolation of cases until the infection is controlled adequately. These measures certainly reduce the risk of occult nosocomial tuberculosis considerably.[14,15]

Creutzfeldt-Jakob disease (CJD) is another example of a disease for which nosocomial transmission may be difficult to trace. Inappropriate sterilization of surgical instruments, contaminated human growth hormone, and corneal transplants have been implicated in such cases.[16,17] The investigations of these outbreaks have shown that recognition of the problem has taken months to years and has been difficult because of the long incubation of the disease and because some patients already may have died before recognition of problem. Because inactivation of prions requires special sterilization and disinfection procedures, and because no one knows how many persons are potentially incubating the new variant of CJD, very careful surveillance and control programs should be implemented in order to detect and prevent potential nosocomial transmission, whether by instruments or by other routes such as grafts or, potentially, by transfusion. A recent report on 405 patients who were part of population-based studies done between 1993 and 1995 in Europe showed that a history of surgery or medical treatment was not a risk factor for CJD.[18]

INFECTIONS DIFFICULT TO DIAGNOSE

Although many infectious diseases can be picked up by standard microbiological tests, some agents may be difficult to detect, either because deep specimens need to be obtained or because specific tests should be ordered. For example, invasive aspergillosis is difficult to diagnose, especially at an early stage. Only tissue specimens can provide definite proof and often cannot be obtained, even if the diagnosis is suspected. Invasive aspergillosis often is an autopsy finding. Given the declining rate of autopsies in many centers and the widespread use of empirical antifungal therapy, the true incidence of aspergillosis may be grossly underestimated.

It is estimated that viruses contribute to at least 5% of all nosocomial infections,[19] but this is probably an underestimate, because appropriate diagnostic tests may not exist or may not be ordered, especially because they are expensive and often have no therapeutic implications. With the continued development of rapid viral diagnostic methods and antiviral chemotherapy, it is likely that viral noso-

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comial infection will be recognized increasingly.

Another example of a nosocomial infection that may be unrecognized is *Legionella pneumophila.* We recently encountered such a situation in our onco-hematological unit. For many years, the water system was monitored for the presence of *L pneumophila,* according to the methods proposed by the CDC, and no *Legionella* species were found. After the discovery of two cases with positive cultures diagnosed 18 months apart but harboring the same pulsed-field gel electrophoresis pattern, we initiated a retrospective sero-epidemiological study, taking advantage of the fact that weekly serum samples are obtained and frozen from patients hospitalized in this unit. Among 153 hospitalized and investigated patients during an 18-month period, 7 additional cases of legionellosis were diagnosed on the basis of a fourfold increase in antibody titers during hospitalization. Clinically, these cases presented as a febrile neutropenic episode and were treated empirically, without specific tests ordered for the detection of *Legionella.* This illustrates that an unremarkable clinical presentation and an environmental control of insufficient sensitivity may hamper proper recognition of a problem due to certain pathogens such as *Legionella* species.

Finally, inadequate laboratory methods may account for underdiagnosed or unrecognized nosocomial infections or problems. A typical example is the use of suboptimal methods for the detection of antibiotic resistance, such as methicillin-resistance in *Staphylococcus aureus.*

SHORT HOSPITALIZATION STAY

During the last 15 years, there has been a considerable reduction in the mean duration of hospital stay due to cost constraints and improvements in the healthcare delivery system; however, the incubation time of infectious diseases has not changed. Because many diagnostic and therapeutic procedures that are risk factors for infections are performed during the first few days of hospitalization, the reduced duration of the hospital stay will result in an increasing proportion of patients becoming symptomatic after discharge. This problem typically is illustrated by infections of the surgical site.[20] Only a surveillance program including an active and systematic tracing of infections will uncover infections that may become symptomatic after discharge, and patients may not necessarily come back to the same hospital if they develop an infection.

DIFFICULTY IN DIFFERENTIATING NOSOCOMIAL FROM COMMUNITY-ACQUIRED INFECTIONS

For some infections, it may be difficult to differentiate nosocomial from community acquisition, especially when an epidemic is ongoing in the community. Typical examples are influenza virus, respiratory syncytial virus, and rotavirus infections.[21,22] In fact, any disease that can be acquired in the community also potentially can be acquired in hospitals if the appropriate mode of transmission exists. This was illustrated above with the examples of tuberculosis and bloodborne viruses.

TABLE 2
POTENTIAL CONSEQUENCES OF OCCULT NOSOCOMIAL INFECTIONS

Infection of the patient
Inadequate assessment of the problem with inappropriate preventive measures
Transmission to other patients or to healthcare workers
Transmission to the family, etc
Inappropriate attribution of costs

For certain infections, the reservoir and the mode of transmission are not known exactly, and existence of nosocomial acquisition is controversial. This is illustrated by the case for *Pneumocystis carinii.* The reservoir of human pneumocystosis is believed to be the human being, but human-to-human transmission never has been proven. Clinical cases are believed to result either from reactivation or from the recent acquisition of *P carinii.* Clusters of cases observed in hospitals have been described, but the exact epidemiological link between cases has not been elucidated. At this stage, there are no firm recommendations for limiting transmission in hospitals.[23] The issue of cross-contamination should be investigated further in order to define the reservoir and route of transmission better and to establish the real proportion of cases that may be considered as nosocomial.

COLONIZATION

Unrecognized colonization is a very important determinant of nosocomial infections, particularly with multiresistant pathogens such as methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Readmitted patients colonized with MRSA are known to be one of the main sources contributing to persistence of MRSA in hospitals. Surveillance of colonization by certain pathogens is an impossible task, except in some limited and targeted situations, particularly in case of outbreaks or as a strategy to control MRSA and VRE.

CONSEQUENCES OF OCCULT NOSOCOMIAL INFECTIONS

There are several potential consequences of occult nosocomial infections (Table 2). Inadequate assessment of the problem will result in inappropriate preventive measures. This is illustrated by the *Legionella* cases reported above: in the absence of an identified problem, the environmental monitoring for *Legionella* was thought to be reliable. After identification of the problem, we found that the method proposed by the CDC for water monitoring was not sensitive enough, and we replaced it with swabs of outlets and showers as recently recommended by Yu et al.[24]

Unsuspected asymptomatic infections such as those caused by bloodborne viruses might be transmitted by sexual contacts outside the hospital. Unrecognized tuberculosis

may lead to cases in other patients or healthcare workers. In case an infection is not correctly attributed to a nosocomial origin, the cost might not be charged to the appropriate payer. Finally, the nosocomial origin of certain infections might be found at a later stage and may trigger lawsuits.[18] Transmission of HIV and HCV infections through blood transfusions illustrates this important potential problem.

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Clindamycin Restriction Decreases *Clostridium difficile*-Associated Diarrhea

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Investigators from Hunter Holmes McGuire Veterans' Affairs Medical Center (VAMC) conducted a prospective, observational cohort study to characterize the impact of hospitalwide clindamycin restriction on the incidence of *Clostridium difficile*-associated diarrhea (CDAD).

Clinical data were corrected on hospitalized patients with symptomatic diarrhea, and data on antibiotic use were obtained from hospital pharmacy records. An outbreak of CDAD was caused by a clonal isolate of clindamycin-resistant *C difficile* and was associated with increased use of clindamycin. Hospitalwide requirement of approval by an infectious disease consultant of clindamycin use led to an overall reduction in clindamycin use, a sustained reduction in the mean number of cases of CDAD (11.5 cases/month vs 3.33 cases/month; $P<.001$), and an increase in clindamycin susceptibility among *C difficile* isolates (9% vs 61%; $P<.001$). Although a parallel increase was noted in the use of other antibiotics with antianaerobic activity, including cefotetan, ticarcillin-clavulanate, and imipenem-cilastin, the hospital realized overall cost savings due to the decreased incidence of CDAD.

The authors concluded that hospital formulary restriction of clindamycin is an effective way to decrease CDAD. It also can lead to a return in clindamycin susceptibility among isolates and can effect cost savings to the hospital.

FROM: Climo MW, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM. Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*-associated diarrhea and cost. *Ann Intern Med* 1998;128(12 pt 1):989-995.