Comparative Efficacy of Handwashing Agents against Cytomegalovirus

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ABSTRACT

Conscientious handwashing is often recommended as an important method for limiting transmission of cytomegalovirus (CMV) from infected individuals to health, education, and child care professionals. To assess the efficacy of handwashing, fingertips of radiation-sterilized latex gloves were inoculated with 0.2 mL of ten different CMV strains. Virus in each inoculum was quantitated by plaque assay. After five minutes, viral inocula were allowed to remain (control), or were washed away by dropwise application of 10 mL of distilled water (DI), 5 mL of 0.08% soap followed by 5 mL of DI, 5 mL of 0.01% chlorhexidine gluconate followed by 5 mL of DI, or 5 mL of 0.025% povidone-iodine solution followed by 5 mL of DI. Separate glove fingertips were sampled 5, 15, 30, 60, 120 and 240 minutes after washing and cultured in duplicate for CMV. Similar studies were performed using human cadaver skin. Ordinary soap was as effective at preventing CMV recovery as other more expensive agents. For inocula with <5 $\log_{10}$ pfu CMV/mL, washing with water alone was as effective as other agents. This was confirmed in similar studies with human hands using five CMV stains. Handwashing is probably an effective method for removing CMV from contaminated hands. [Infect Control 1987; 8(4):158-162.]

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Cytomegalovirus (CMV) is a very common pathogen that usually causes minimal or no symptoms in the immunocompetent host. It remains an important cause of morbidity and mortality among unborn fetuses, premature infants, and immunocompromised patients. Though CMV-seropositive blood products and transplanted organs have been associated with transmission of CMV, most people who become infected with CMV have never received blood products or organ transplants. The most important mechanism for CMV transmission worldwide is felt to be prolonged intimate contact with infected secretions or excretions,[1] though a recent study[2] suggests that more casual contact may occasionally result in nosocomial transmission. Most reports suggest that health and child care professionals who work with CMV-infected people are at no greater risk of acquiring CMV disease than persons in the general community,[3-5] but not all investigations support this conclusion.[6] Transmission from infected individuals to potentially pregnant caretakers and indirect transmission via the caretakers from children to other children, pregnant women, or immunocompromised patients remain a concern in many settings.[7]

In the absence of a widely available proven vaccine, current strategies for decreasing the risk of CMV transmission include avoidance of infected secretions and careful handwashing. Since most CMV-infected individuals are asymptomatic and undiagnosed, emphasis on handwashing seems especially important. Despite these recommendations, child care and health personnel in many settings question the efficacy of handwashing against CMV and lobby locally for more restrictive measures when their work brings them in contact with CMV-infected individuals. Those that accept the efficacy of handwashing query which of the many available handwashing agents is best.

To investigate the efficacy of handwashing and handwashing agents against CMV, investigations were performed to determine if handwashing techniques effec-

tively remove CMV from finger-like surfaces, whether handwashing efficacy is dependent on the quantity of virus initially present, and if some handwashing agents are more effective than others against CMV.

METHODS

Virus

Frozen stocks of eight different CMV strains recovered locally from several different types of patients (five asymptomatic congenitally infected infants, two infants with acquired infection, and one adult renal transplant recipient) were used to infect 150 cm^2 confluent monolayers of locally derived human foreskin fibroblasts. None of these strains had been previously passaged more than six times. After two weeks of incubation in 5% CO_2 at 37°C, virus was harvested by scraping each infected monolayer into 10 mL of transport medium (basal medium of Eagle, with 5% fetal calf serum and 100 U penicillin G, 100 micrograms streptomycin, and 2 micrograms amphotericin B per milliliter). Visible cytopathic effect (CPE) at harvest ranged from 20% to 90%. An aliquot was used for viral quantitation and the remainder was employed immediately for inoculation of the experimental surfaces as described below.

As another source of virus, fresh infected urine was obtained from three other infants who had been determined earlier to have asymptomatic congenital CMV infection by isolation of virus from urine obtained at less than one week of age. These infants were 19, 20, and 24 months old when these fresh specimens were obtained. An aliquot of urine was used for viral quantitation and the remainder employed immediately for inoculation of the experimental surfaces.

Viral quantity in fresh infected urine and the recultivated frozen virus harvest was determined by a previously described plaque assay technique.[8]

Recovery of CMV from Glove Fingertips

The fingertips of radiation-sterilized latex gloves were inoculated with 0.2 mL aliquots of the appropriate CMV strain (recultivated frozen virus harvest or fresh infected urine). Five pairs of gloves were used for each strain with six fingertips in each pair receiving inoculum. Gloves were supported on a fenestrated wire screen and small depressions made in the fingertips to accommodate the inocula. Gloves were maintained at ambient temperature (25° to 27°C) and room air. After five minutes, viral inocula were: 1) allowed to remain (control), or were washed away by dropwise application from glass pipettes of, 2) 10 mL of deionized, distilled water (DI), 3) 5 mL of 0.08% Ivory® soap solution (Procter and Gamble, Cincinnati, Ohio) followed by 5 mL of DI, 4) 5 mL of 0.01% chlorhexidine gluconate (2.5 mL of 4% solution in 1000 mL DI; Stuart Pharmaceuticals, Wilmington, Delaware) followed by 5 mL of DI, or 5) 5 mL of 0.025% povidone-iodine skin cleanser solution (2.5 mL of 10% solution in 1000 mL DI; Purdue Frederick, Norwalk, Connecticut) followed by 5.0 mL of DI. Concentrations of handwashing agents had been determined earlier by having people wash their hands in routine fashion with these agents, weighing the reservoirs for the agents before and after use, and measuring the total amount of water used. The mean of three such determinations was used as the study concentration for each handwashing agent.

Separate glove fingertips were sampled with a premoistened sterile cotton swab 5, 15, 30, 60, 120, and 240 minutes after washing. The swabs were then immersed in 2 mL of transport media. Duplicate viral cultures were established with this transport medium. All washed fingertips were visibly dry within 75 minutes of washing; control fingertips with undisturbed viral inocula were all visibly dry within 150 minutes.

Recovery of CMV from Human Skin

Similar studies with three recultivated frozen CMV strains were performed using human skin recovered from autopsy specimens, instead of latex glove fingertips. Skin specimens were from the trunk and were recovered <72 hours after death. Skin specimens were washed with chlorhexidine gluconate, rinsed thoroughly with distilled water, and cut into 1 cm diameter circles. The circles of skin were then placed epidermis up in the depressions of latex glove fingertips as above. Inoculation, washing, and attempted viral recovery were also as described above.

Limited studies were also performed using the hands of the CMV-seropositive author (RGF). Hands were first washed thoroughly with chlorhexidine gluconate and allowed to air dry. On five separate occasions 0.2 mL aliquots of recultivated frozen virus were applied dropwise to the terminal portion of all ten digits. The inocula were allowed to remain as undisturbed as possible on the digits of one hand while the inocula on the other hand were washed away after five minutes by dropwise application of 10 mL of DI to each of the digits. Because of the inherent convexity of the fingertips, much of the inoculum drained down the sides of the digits shortly after inoculation. Viral recovery was attempted as described above, sampling 5, 15, 30, 60, and 120 minutes after washing. All digits were visibly dry within 15 minutes of washing.

Virology

Confluent monolayers of locally prepared human foreskin fibroblasts were inoculated in duplicate and were observed for the characteristic cytopathic effect of CMV. Cultures were examined twice weekly for four weeks before being discarded.

RESULTS

CMV could be recovered from glove fingertips under control conditions for periods ranging from 15 to 240 minutes (Table 1). In general, the greater the amount of virus present in the inoculum, the longer the virus could be recovered (Pearson's correlation coefficient $r = +0.85$; $P<0.01$ by t test). After washing with soap, chlorhexidine or povidone-iodine, no CMV could be recovered at any time. Fibroblasts in the inoculated culture tubes remained healthy and should have been able to display cytopathic effect. When distilled water alone was used for washing, no CMV could be recovered at any time with eight of the ten strains; in the two strains with the most virus present in the inoculum (log_{10}pfu/mL 5.7 and 6.0), CMV could be recovered at five minutes, but no later. There were no apparent differences whether recultivated frozen virus or

TABLE 1
RECOVERY OF VIRUS FROM LATEX GLOVE FINGERTIPS AFTER WASHING WITH SELECTED HANDWASHING AGENTS

	Reactivated Frozen Stocks							Fresh Infected Urine		
CMV Strain	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**	**C**
Log_{10} pfu/mL	5.7	4.9	3.9	6.0	4.2	2.7	3.5	3.1	2.7	4.0
SD	±0.9	±0.5	±0.5	±0.8	±0.4	±0.3	±0.4	±0.2	±0.3	±0.6
Latest CMV recovery (minutes)										
Control	240	120	30	120	60	15	15	15	15	30
DI	5	N	N	5	N	N	N	N	N	N
S + DI	N	N	N	N	N	N	N	N	N	N
C + DI	N	N	N	N	N	N	N	N	N	N
I + DI	N	N	N	N	N	N	N	N	N	N

N = Not recovered
DI = Deionized, distilled water only
S + DI = Soap followed by distilled water
C + DI = Chlorhexidine gluconate followed by distilled water
I + DI = Povidone-iodine followed by distilled water

TABLE 2
RECOVERY OF VIRUS FROM HUMAN SKIN AFTER WASHING WITH SELECTED HANDWASHING AGENTS

	Cadaver Skin			Live Skin				
CMV Strain	**1**	**4**	**8**	**1**	**2**	**4**	**6**	**7**
Log_{10} pfu/mL	5.5	5.9	2.9	5.2	4.7	5.2	4.0	3.1
SD	±0.8	±0.6	±0.3	±1.0	±0.8	±0.7	±0.5	±0.5
Latest CMV recovery (minutes)								
Control	120	120	15	30	30	30	15	5
DI	5	5	N	N	N	N	N	N
S + DI	N	N	N	—	—	—	—	—
C + DI	N	N	N	—	—	—	—	—
I + DI	N	N	N	—	—	—	—	—

N = not recovered
DI = deionized, distilled water only
S + DI = soap followed by distilled water
C + DI = chlorhexidine gluconate followed by distilled water
I + DI = Povidone-iodine followed by distilled water
— = not performed

fresh infected urine was used as the inoculum. Similar results were obtained when attempts were made to recover CMV from human skin (Table 2).

DISCUSSION

This study suggests that handwashing is an effective means of eradicating CMV from the hands of contaminated caretakers. Ordinary hand soap appeared to be as effective as other more expensive handwashing agents. For inocula with less than 5 log_{10} pfu CMV/mL, washing with water alone may be as effective as other agents.

Avoidance of direct contact with CMV-infected secretions and excretions is desirable but not always feasible. Hutto has previously demonstrated that CMV could be recovered from the hands of two children and one teacher during a random survey in a day care center; restriction enzyme analysis demonstrated the virus from the hands of the teacher to be identical to that in the saliva from one child.[9] Though transmission of CMV to a caretaker by hand-to-mucosa contact or to another person by contaminated caretaker or patient hands has not been proven, such routes have been established for other viral pathogens[10,11] and are felt by many investigators to be possibly important in person-to-person transmission of CMV.[12-14] Effective removal of virus from the hands promptly after contact with contaminated secretions or excretions may be an important step in preventing such transmission.

The present investigation is limited by the fact that real human fingers were used in only a portion of the studies. The gloves and prewashed human skin from autopsy specimens lacked the oils, natural lubricants, usual resident microflora, and other local microenvironmental fac-

tors present in vivo. Use of these artificial models reduced the probability of obtaining coexistent bacterial contaminants and toxic substances when sampling the inoculated site; such contaminants may have disrupted the fibroblast monolayer and made cytopathic effect undetectable. Detection of residual virus on the experimentally contaminated "skin" surfaces by viral culture may not be as sensitive as other more complex techniques, such as DNA hybridization.[15] It is possible that live CMV may have persisted on the washed "skin" surfaces in quantities too small to be detected by viral culture. The critical quantity of CMV necessary for human infection and its ability to cause discernible CPE on tissue culture is unknown. It is notable that in the limited studies with real human fingers, viral recovery was attained from the unwashed fingers for shorter periods than when the same viral strains in comparable quantities had been studied on glove fingertips. Whether this reflects loss of initial inoculum by dripping down convex fingertips, more rapid drying because of higher temperature in the real fingers, or other factors is unclear.

In actual practice, handwashing is usually more vigorous than in the present study. Handwashing agents and rinse water are neither applied dropwise nor in the limited volumes used in this study. It is also unlikely that the quantities of contaminated secretions used in this study would be allowed to remain in place for five minutes before attempts at washing are made. Many CMV-infected persons shed virus in much smaller quantities than those used here. It seems probable that usual handwashing technique would be even more effective for eliminating CMV from contaminated hands than indicated by the present results.

It cannot be concluded that there is no need for the use of any handwashing agents other than soap and water, since there may be other pathogens of concern that may require other agents. Similarly, even if CMV is the major pathogen of concern, the use of water alone cannot be recommended despite its apparent efficacy against lower concentrations of virus. The results do suggest, however, that in the absence of soap or other agents, rinsing vigorously with water will limit persistence of virus at the contaminated site.

Handwashing studies may be complicated by residual soap or disinfectant being carried into culture medium when hands are cultured after washing with the soap or disinfectant. This transfer of residual handwashing agent prolongs the contact time between the target organism and the handwashing agent and may artificially exaggerate inhibitory action. One strategy commonly used to overcome this potential problem is to massively dilute the inoculum that potentially contains the residual soap or disinfectant. In the present study, the initial application of handwashing agent was rinsed with an equal volume of DI. The rinsed surface was then sampled with a premoistened swab. Studies with dry swabs indicate that the swabs used in this study can absorb a maximum of 150 mg of fluid from the rinsed experimental surface; premoistened swabs probably absorb considerably less. The swab was then placed in 2 mL of transport media, 0.75 mL of which was then added to each of two viral culture tubes containing 2.25 mL of tissue culture media. This successive rinsing and dilution results in a possible maximal concentration of handwashing agent in the viral culture tube that is only 0.875% of that on the experimental surface. Since the quantity of fluid absorbed by the premoistened swabs in this study is probably considerably less than that used in calculating this estimate, the actual final concentration of residual handwashing agent in the culture tube is probably even lower. Existing data does not allow a guarantee that such dilution is adequate to absolutely preclude artificial prolongation of contact time between CMV and the handwashing agents, but the greater than one hundredfold dilution certainly decreases the probability of such artifact.

The inability to recover CMV after washing could also reflect direct killing of virus, dilution of viral concentration below a critical infectious dose, or merely the physical removal of the virus from the inoculated surface. To clarify this issue, attempts were made to recover CMV from the wash fluids drained off the glove tips and human cadaver skin. These attempts were unsuccessful because the undiluted drainage fluids almost uniformly induced toxicity in the fibroblast monolayers of the culture tubes, making detection of CPE impossible. Such toxicity was not surprising in view of the nonphysiologic osmolarity and pH of the drainage fluids. It seems unlikely that distilled water alone should kill the virus since a previous study has demonstrated that distilled water stabilizes human CMV at both 4°C and 37°C.[16] The unknown mechanism by which handwashing eradicates the virus may influence the respect with which one handles the drained fluid, but does not alter the observation that virus can no longer be recovered from the hands after washing.

Handwashing is an effective means of removing CMV from contaminated hands and may therefore be a reliable technique for decreasing the risk of human CMV transmission in some settings. Since infected individuals are often asymptomatic and are very common in the community, it makes sense to be liberal in washing hands and other skin surfaces that contact potentially infected secretions or excretions in any setting. Careful attention to washing all potentially contaminated skin surfaces, rather than a quick, cursory technique, is probably an important factor in removing CMV. The choice of handwashing agent does not appear to be a critical factor.

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Evaluation of a Handwashing Intervention to Reduce Respiratory Illness Rates in Senior Day-Care Centers

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ABSTRACT

To decrease respiratory infections in senior day care, staff were educated on viral transmission and the value of hand washing. Fanny packs with alcohol foam supplemented hand washing and were alternated monthly between centers. Infection rates were unchanged with alcohol foam use. The intervention year's infection rate was significantly lower than the previous 3 years, suggesting a benefit of education (*Infect Control Hosp Epidemiol* 1999;20:200-202).

Acute respiratory illnesses are a major cause of morbidity in persons of all ages. Although rates of respiratory infections generally decline with advancing age, their impact may be much greater in older persons.[1-4] Lower rates of respiratory infections in older persons may be due in part to less frequent exposures to pathogens. Adult day-care centers have gained popularity as an alternative to institutionalizing frail elderly. Similar to the situation with children in day care, acute respiratory infections in elderly day-care attendees are common, and nosocomial spread of respiratory viruses occurs.[2] In the present study, we assessed the value of a staff educational program combined with the use of a portable virucidal foam for the reduction of respiratory infections in day-care participants.

METHODS

Location and Subjects

The study was conducted at three adult day-care centers located in Rochester, New York. The centers all have similar facilities and provide comprehensive services to frail elderly who are nursing home eligible by New York Medicaid standards. All new staff undergo basic infection control training that includes education on Universal Precautions, transmission of common organisms, and isolation procedures. Day-care policy instructs staff with febrile respiratory illnesses to stay home from work. Each center has approximately 70 elderly day-care participants, with a mean age of 79 years. The number of staff at each center varied from 20 to 45. Approximately 90% of the staff are women, with a mean age of 36 years.

Study Period

Surveillance of respiratory infections was performed from December 1992 through March 1996. The intervention took place during a 4-month period from December 1, 1995, through March 30, 1996.

Surveillance

An acute respiratory illness was defined during all 4 years of surveillance as nasal congestion, sore throat, new or increased cough, wheezing, sputum production, or respiratory difficulty with or without fever. Surveillance among participants was carried out by the day-care staff and reported to two study nurses. Illnesses in staff were self-reported. An illness evaluation consisted of a directed history, physical examination, nasopharyngeal swabs for viral culture, and the collection of acute and convalescent sera.

Study Design

During the last week of November 1995, a 1-hour educational session discussing the transmission of respiratory viruses and the importance of hand washing was held at all centers. Each staff member received an informational sheet containing an electron micrographic picture of the respiratory viruses, the associated clinical syndromes, and modes of transmission.

Supplemental Intervention

During the period of supplemental intervention, all staff with patient contact were given a fanny pack containing virucidal alcohol foam (Alcare Plus, Calgon Vestal Laboratories, St Louis, MO). Staff were instructed to use the alcohol foam after each interaction requiring hands-on contact with participants or if they coughed or sneezed into their own hands. They were instructed to wash their hands with soap and water at a sink as they normally would and that use of the alcohol foam was to supplement hand washing at sinks, not to replace it. To minimize the impact of center differences, the sites of the supplemental intervention were rotated on a monthly basis. All centers had 2 months of intervention and 2 months without intervention. Rates of infection during supplemental intervention from all centers were compared with rates of infection during non-intervention periods. To assess the effects of the educational program, infection rates during the 4-month period from centers 1 and 2 were compared with data from the 1992 to 1993, 1993 to 1994, and 1994 to 1995 seasons at those same centers. Center 3 was not included in this analysis because it was opened in 1994.

Statistics

A Poisson regression model was fit to explain numbers of infections as a function of center, status as participant or staff, month, year, and whether the intervention

TABLE 1
VIRAL PATHOGENS IDENTIFIED IN ELDERLY PARTICIPANT AND STAFF RESPIRATORY ILLNESSES

	1992-1993		1993-1994		1994-1995		1995-1996	
Pathogen	Elderly	Staff	Elderly	Staff	Elderly	Staff	Elderly	Staff
Influenza A	10	7	5	5	1	2	5	2
Influenza B	6	4	0	1	0	2	0	1
RSV	8	3	13	2	7	3	6	1
Coronavirus OC43	11	1	4	1	11	0	7	1
Coronavirus 229E	14	10	4	0	6	7	0	0
Parainfluenza	2	0	2	0	2	2	2	1
Rhinovirus	0	2	3	2	6	4	0	0
Unknown	27	19	45	28	41	21	15	25
Total illnesses*	70	42	73	39	67	39	31	31

Abbreviation. RSV, respiratory syncytial virus.
* Some illnesses were associated with more than one viral infection.

was in progress. Allowance was made for the dependence between multiple observations on the same individual. Significance levels were computed by comparing estimates to their asymptotic variances and covariances.

Laboratory Methods

Viral cultures were done using WI-38, HEp-2, and primary rhesus monkey cell lines and standard methodology. Serological evidence of infection was defined as a fourfold rise in IgG as measured by enzyme immunoassay to the following viruses: influenza A and B, parainfluenzas 1, 2, and 3, respiratory syncytial virus, and coronaviruses 229E and OC43.[3]

RESULTS

Intervention, 1995 to 1996

To assess the overall effect of staff education and the supplemental intervention, infection rates at centers 1 and 2 during the 1995 to 1996 season were compared with historical data from the three previous winter seasons. The number of participants and staff increased slightly at both centers over the 4-year period. To adjust for variability in participant and staff attendance at each day-care center during each month of study, rates of infection were calculated and expressed as infections per 100 person-months. The rates of infection among the day-care participants were not significantly different during the first 3 years (14.5, 12.8, and 10.4/100 person-months). In the final intervention year, the infection rate fell to 5.7 per 100 person-months ($P<.0001$, compared to the three previous seasons' rates). The rate of infections among staff members was higher in year 1 (21.0), but was not significantly different in years 2 to 4 (13.9, 11.3, and 9.5/100 person-months).

Although there was variability in the specific pathogens that were identified among participants and staff (Table 1), no difference in etiologies was noted that would account for the drop in the infection rate in year 4. With the exception of the first year, there were relatively few influenza virus infections at any of the centers.

Supplemental Intervention

The effect of the virucidal foam was evaluated by combining the data from all three centers. Rates of infection were compared during time on intervention versus time not on intervention. No significant difference in illness rates, expressed as infections per 100 person-months, was noted for participants (8.27 vs 7.04, $P=.64$) and staff (16.8 vs 17.6, $P=.148$). The actual number of infections per center per month for participant and staff during the period of supplemental intervention is shown in Table 2.

DISCUSSION

The development of adult day-care centers has been a successful strategy for the management of a growing frail, elderly population.[5] However, attendance in day care may expose frail older persons to an environment where transmission of infectious agents is more common.[2,6,7] With the exception of influenza virus, most common respiratory viruses are spread by fomites and direct inoculation. Thus, hand washing should be a critical infection control strategy to limit nosocomial spread.[8]

We found that an educational program for staff at the start of the 1995 winter season was associated with an almost 50% decrease in the infection rate in day-care attendees during the following 4-month period. The use of historical data for controls can be problematic, especially considering the epidemic nature of respiratory viruses. The infection rate among staff during the 1995 to 1996 season was not reduced substantially, indicating that it was not an unusually mild year for respiratory infections. There was a gradual decline in infections among the day-care participants during the three seasons prior to the intervention. This may have been due to the development of immunity with repeated infections, as seen in children attending day care for a prolonged period[6]; the average time enrolled in the program increased from 0.76 years in 1992 to 1.9 years in 1995. However, the infection rate during the intervention year showed a highly statistically significant difference from prior years, suggesting that the lower rate did not simply reflect the continued downward trend.

TABLE 2
ILLNESSES IN PARTICIPANT AND STAFF BY CENTER AND MONTH DURING THE 1995 TO 1996 INTERVENTION SEASON

	Number Ill/Number in Group (%)					
	Center 1		Center 2		Center 3	
	Elderly	Staff	Elderly	Staff	Elderly	Staff 3
December	3/69 (4%)	5/36 (14%)	2/67 (3%)	1/45 (2%)	1/68* (2%)	6/16* (38%)
January	11/70* (16%)	7/36* (19%)	1/67* (2%)	2/45* (4%)	5/70 (7%)	6/17 (35%)
February	4/69 (6%)	5/37 (14%)	2/61 (3%)	4/46 (9%)	4/70* (6%)	1/17* (6%)
March	4/77* (5%)	3/37* (8%)	4/65* (6%)	3/45* (7%)	3/69 (4%)	4/18 (22%)

Data shown as number of illnesses/number of elderly participants or staff in attendance.
* Indicates that the staff at that center were using the supplemental intervention during that month.

Because the number of handwashing episodes among staff were not specifically measured during this study, it is not possible to conclude that increased hand washing was directly responsible for the decline in infections among elderly day-care attendees. Indeed, the lower infection rate likely reflected the combination of the interventions and education, which increased staff awareness and more broadly changed behavior. There was no apparent additional benefit from the virucidal foam. Because the rates of respiratory illness were much lower at all centers during the intervention year, it is possible that any potential effect of the foam was hidden by the other simultaneous changes.

In conclusion, re-education of staff each winter season on the transmission of the "common cold" viruses and the benefits of frequent hand washing may help to limit the spread of these pathogens.

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Regional Dissemination and Control of Epidemic Methicillin-Resistant *Staphylococcus aureus*

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ABSTRACT

A methicillin-resistant *Staphylococcus aureus* (MRSA) strain introduced into the largest tertiary-care teaching hospital in Manitoba in 1993 led to a sustained outbreak with secondary outbreaks at one community hospital, two large long-term–care facilities, and nosocomial transmission at a second teaching hospital. Control measures were consistent at each institution and were coordinated on a province-wide basis. MRSA is not currently endemic in any facility in the province (*Infect Control Hosp Epidemiol* 1999;20:202-205).

Nosocomial outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) with strains characterized by efficient transmission in the institutional setting have been reported repeatedly.[1] Intensive measures are recommended to control such outbreaks within an institution, although eradication often is not achieved.[2] Epidemic strains frequently will disseminate among institutions in a region.[3-5] There is little information describing efforts of control and eradication on a regional, rather than institutional, basis. In 1993 an outbreak of MRSA occurred at our institution with a strain originally imported from the Punjab to another facility in Canada.[6] This report describes the further spread of this outbreak strain to other local institutions and coordinated regional efforts of control, which appear to have been effective.

REGION

The province of Manitoba has a population of approximately 1.1 million, over one half of whom reside in Winnipeg. This outbreak initially occurred at the Health Sciences Centre (HSC), an 830-bed tertiary-care teaching hospital. Other institutions in the city include a second teaching hospital with some tertiary-care activities, five community hospitals, and three large (>100 beds) geriatric and reha-

Molecular Epidemiology of "Norwalk-like Viruses" in Outbreaks of Gastroenteritis in the United States

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Fecal specimens from 90 outbreaks of nonbacterial gastroenteritis reported to 33 state health departments from January 1996 to June 1997 were examined to determine the importance of and to characterize "Norwalk-like viruses" (NLVs) in these outbreaks. NLVs were detected by reverse transcription–polymerase chain reaction in specimens from 86 (96%) of 90 outbreaks. Outbreaks were most frequent in nursing homes and hospitals (43%), followed by restaurants or events with catered meals (26%); consumption of contaminated food was the most commonly identified mode of transmission (37%). Nucleotide sequence analysis showed great diversity between strains but also provided evidence indicating the emergence of a common, predominant strain. The application of improved molecular techniques to detect NLVs demonstrates that most outbreaks of nonbacterial gastroenteritis in the United States appear to be associated with these viruses and that sequence analysis is a robust tool to help link or differentiate these outbreaks.

"Norwalk-like viruses" (NLVs), also called small round-structured viruses, are a group of genetically diverse, single-stranded RNA viruses belonging to a newly proposed genus in the family Caliciviridae that are recognized as an important cause of outbreaks of acute nonbacterial gastroenteritis [1–3]. Such outbreaks have been reported in a variety of settings, including nursing homes [4–6], hospitals [5, 7, 8], cruise ships [9–12], schools and universities [13, 14], and restaurants and events with catered meals [15–17]. Transmission of the viruses has been documented by contaminated food [8, 15, 18, 19], especially oysters [20–24] and water [25–28], and by person-to-person contact [11, 29, 30].

NLVs can be divided into two distinct genogroups, genogroup I (GI) and genogroup II (GII) [31], each of which can be further divided into 4 and 6 clusters, respectively. GI includes the Norwalk virus, Southampton virus, cruise ship virus, and Desert Shield virus clusters. GII includes the Gwynedd virus, Toronto virus, Lordsdale virus, Snow Mountain agent, and White River and Hawaii virus clusters [32]. Several reports have described the predominant circulation of strains in a particular cluster [5, 33, 34], and Vinje et al. [5] recently reported both a single predominant strain and a shift in predominant clusters over time. The development of sensitive reverse transcription–polymerase chain reaction (RT-PCR) has improved the detection rates for NLVs in outbreaks of gastroenteritis to as high as 91% in a study conducted in The Netherlands [6]. Sequence analysis not only allows for examination of circulating strain types but also has been used to aid in epidemiologic investigations by linking or differentiating outbreaks [35]. Whereas there have been studies examining the role and molecular characteristics of NLVs in outbreaks of nonbacterial gastroenteritis in other countries [5, 6], this analysis has not been done previously in the United States.

In this study, we examined a collection of fecal and emesis specimens from 90 outbreaks of nonbacterial gastroenteritis reported to the Centers for Disease Control and Prevention (CDC) by state and local health departments during an 18-month period between January 1996 and June 1997. For each outbreak, epidemiologic data were recorded, and RT-PCR and nucleotide sequencing studies were performed on the stool and emesis samples. This unique combination of epidemiologic and molecular data has allowed us to examine the role of NLVs in outbreaks of nonbacterial gastroenteritis in the United States, the distribution of strains circulating over time and geographic location, and the patterns of illness with respect to settings, modes of transmission, ages of persons affected, and size of outbreaks. We also assessed several outbreaks in which the molecular data aided the classic epidemiologic investigation by either reenforcing the epidemiologists' conclusion or by conflicting with it and thereby encouraging the investigator to examine the data for other conclusions.

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Table 1. Epidemiologic characteristics of 90 outbreaks of gastroenteritis investigated in the United States, January 1996 to June 1997.

Setting	No. of outbreaks (%)	Mean age (range)	Mode of transmission						Median (range)	
			F	PP	O	W	U	No data	Persons affected	Persons at risk
Nursing homes, retirement centers, and hospitals	39 (43)	81 (23–101)	2	8	0	0	9	20	41 (24–151)	147 (30–780)
Restaurants and events with catered meals	23 (26)	37 (0.9–72)	13	0	0	0	1	9	44 (10–6000)	120 (14–12,000)
Oyster consumption	5 (6)	43 (24–49)	0	0	5	0	0	0	215 (75–233)	233[a]
Schools and day care centers	10 (11)	16 (0.5–52)	3	0	0	2	2	3	72 (14–629)	116 (17–1657)
Vacation settings (including cruise ships)	10 (11)	44 (1–77)	1	2	0	1	2	4	354 (54–642)	1154 (121–55,456)
Other[b]	3 (3)	35 (24–50)	0	0	0	0	0	3	109 (60–157)	960[a]
Total (%)[c]	90 (100)	54 (0.5–101)	19 (37)	10 (20)	5 (10)	3 (6)	14 (27)	39	53 (10–6000)	150 (14–55,456)

NOTE. Data were not available in all categories for all outbreaks. Mode of transmission: F, foodborne; PP, person-to-person; O, oyster-associated; W, waterborne; U, undetermined.

[a] Data from only 1 outbreak.

[b] "Other" includes 2 outbreaks in prisons and 1 in a homeless shelter.

[c] Percentages of each mode of transmission were determined using only outbreaks for which data were available and excluding those in "no data" category.

Materials and Methods

Outbreaks and specimens. Between January 1996 and June 1997, 120 outbreaks of nonbacterial gastroenteritis were reported to the CDC by 33 state and local health departments. Many states ($n = 14$) reported only a single outbreak, and 1 state, Florida, reported 29 outbreaks. For each outbreak, the epidemiologist was requested to provide information on the setting, date, presumed mode of transmission, number of persons affected and at risk, symptoms, and ages of patients. Oyster-associated outbreaks were classified separately from other foodborne outbreaks to reflect the differences in how each is contaminated; oysters are typically contaminated before harvest and distribution, whereas in many other viral food-related outbreaks, the contamination can be linked to an ill food handler or other on-site contamination. We examined a subset of 90 outbreaks for which (1) epidemiologic data were available, (2) laboratory tests were negative for bacterial and parasitic agents, and (3) at least 4 stool or emesis samples had been collected in a timely fashion (within 48–72 h after onset), stored at 4°C with no preservatives [36], and submitted to our laboratory. Each outbreak was identified by a unique number and 4-letter code. All specimens with adequate testing volume were examined in outbreaks with ≤20 specimens, and 20 specimens were chosen for testing when >20 were submitted.

Detection and genetic characterization of NLVs. Specimens from all outbreaks were examined by RT-PCR using two primer sets, G-1 and G-2 [37], which amplify a 123-base region of the polymerase gene of GI and GII viruses, respectively. At least 1 RT-PCR–positive specimen from each outbreak was genetically characterized by nucleotide sequencing of both strands of the amplified 123-bp product [37], using an ABI PRISM Dye Terminator Cycle Sequencing Kit with AmpliTaq DNA Polymerase (Perkin-Elmer, Foster City, CA) on an automated sequencer (model 377; Applied Biosystems, Foster City, CA). After removal of primer sequences, the unique 81 bases from each of 86 outbreak strains, 10 reference strains from GenBank, and 15 previously characterized UK strains [37] were analyzed by using the GCG suite of programs [38]. Strain diversity was estimated using the DISTANCES program with the Jukes Cantor method. A phylogram was created using the GROWTREE program with the neighbor-joining method. The phylogram was used to classify strains into 1 of 10 presumed antigenic clusters [32]. A small subset of strains that could not be amplified in the polymerase region or characterized into an antigenic cluster on the basis of the 81-base nucleotide sequence of the polymerase gene was further examined by amplifying a 322-base region of the capsid gene, using two additional primers, MON381 and MON383 [32]. After classifying strains into clusters based on the phylogram, we examined the strain distribution over time, looked for predominant strains or clusters during the period of investigation, and used the nucleotide sequence information to aid in outbreak investigations by comparing conclusions based on molecular data with those of the classic epidemiologic investigation.

Because the region of sequence examined in this study is small, the sequences have not been submitted to GenBank. The sequences are available upon request. GenBank accession numbers for reference strains used in this analysis are Camberwell virus, U46500; Desert Shield virus, U04469; Hawaii virus, U07611; Lordsdale virus, X86557; Melksham virus, X81879; Mexico virus, U22498; Norwalk virus (NV), M87611; Snow Mountain agent, L23831; Southampton virus, L07418; and Toronto virus, U02030.

Results

Epidemiologic characteristics of outbreaks. We examined the epidemiologic characteristics of 90 outbreaks of nonbacterial gastroenteritis by setting, ages of patients, presumed mode of transmission, and numbers of persons affected and at risk in each outbreak (table 1). These outbreaks occurred in 33 states and in many different settings; nursing homes were the most common (43%), followed by restaurants and events with catered meals (26%). Persons of all ages, from 6 months to 101 years, were affected (average age, 54 years). Outbreak size ranged from small clusters, of 10 people, to epidemics involving >6000 persons, and the numbers of persons at risk ranged from 14 at a family gathering to 55,456 people at a hotel with 3000 guests, in which the outbreak persisted for 34 days. Of the 51 outbreaks

for which the mode of transmission was reported, foodborne spread was the most common (37%), followed by person-to-person contact (20%), ingestion of contaminated oysters (10%), and consumption of contaminated water (6%); for many outbreaks, the specific mode of transmission was sought but could not be determined (27%). Of note, person-to-person contact is often a diagnosis of exclusion when other modes cannot be clearly identified. Nursing homes were the setting in which epidemiologists were least able to determine a specific mode of transmission (47%, 9/19 outbreaks). The crude attack rates ranged from 1.2% to 93%, probably because of differences in the thoroughness of the epidemiologic investigation, as some outbreaks were actively investigated by a CDC or state epidemiologist, and some were passively reported to state health departments with less investigation.

Laboratory results. A total of 1084 stool or emesis specimens were received from 90 outbreaks (median, 8.5 specimens per outbreak; range, 4–71). Of these, 901 were suitable for testing by RT-PCR (median, 8 specimens per outbreak; range, 4–38), using both the G-1 and G-2 primer sets. NLVs were detected in at least 1 specimen from 86 outbreaks (96%), and detection rates within outbreaks ranged from 11% (1/9 specimens) in 1 outbreak to 100% in 6 outbreaks. A total of 442 specimens (49%) were positive by RT-PCR, including 424 (96%) that were positive with the G-2 primer set and 18 (4%) with the G-1 primer set.

The RT-PCR product from at least 1 representative strain from each of 86 NLV-positive outbreaks was sequenced, and a rooted dendrogram of genetic distances was constructed (figure 1). The 86 outbreaks were characterized into genetic clusters as defined by Noel et al. [32], rather than probe types, as used previously for polymerase sequences, because not all outbreak specimens were examined by Southern hybridization. Strain clustering in the dendrograms based on the polymerase and capsid regions correlated well with each other with one exception: In the polymerase region, Snow Mountain agent and Melksham virus segregated into separate clusters, whereas in the capsid region, they formed a single cluster. This discrepancy is most likely due to the small region of sequence used for the polymerase analysis, so we have chosen to consider them a single cluster on the basis of the larger capsid sequence. Additionally, the polymerase dendrogram has been simplified by labeling the Norwalk, Southampton, cruise ship, and Desert Shield virus clusters as NV because we detected few of these strains in this study. Using these parameters, we were able to characterize the strains in this study period into 6 clusters: NV, Gwynedd virus, Toronto virus, Hawaii virus, Lordsdale virus, and Snow Mountain agent. No strains representative of the White River cluster were detected during this study period. Overall, the diversity was great between strains, with two exceptions. In the Lordsdale cluster, over the 18-month period of the study, a "common" strain with identical 81-base nucleotide sequence caused 29 (32%) of the 90 outbreaks. This common strain was first identified in April 1995 and, during this study period, was identified from outbreaks in 15 states as geographically disperse as Florida, Alaska, and Hawaii, with no epidemiologic link apparent between the outbreaks it caused. Similarly, in the Toronto cluster, 8 outbreaks were caused by strains with identical sequence. Within other clusters, all strains, except 2 in the Hawaii virus cluster, could be differentiated on the basis of the 81-base nucleotide sequence.

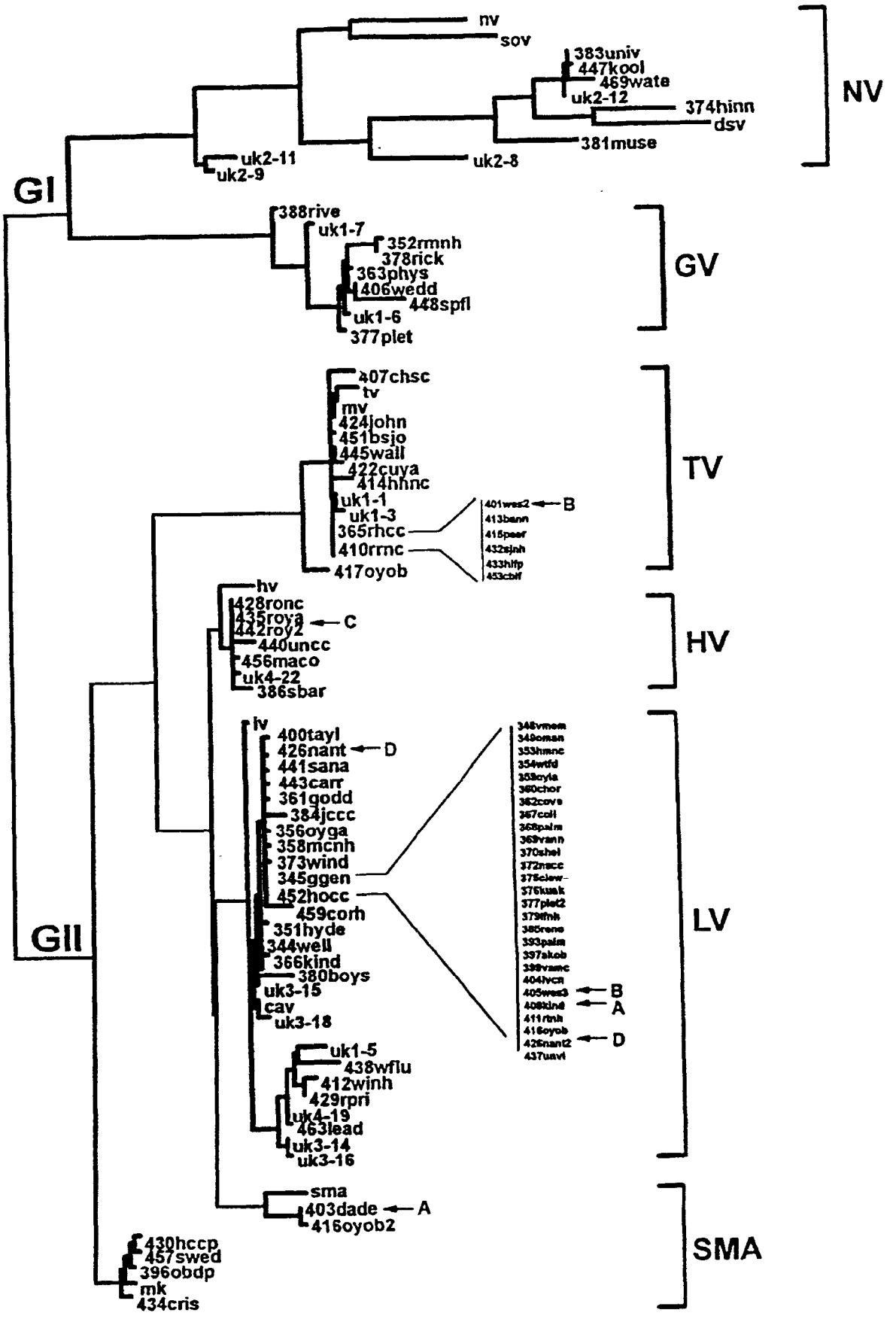
To further investigate trends of epidemic strains over time, we examined the quarterly distribution of outbreak strains spanning the 18-month study period (figure 2). This analysis was done using a denominator of 92 strains, rather than 90 outbreaks, because multiple strains of virus were identified in 2 outbreaks. The Lordsdale virus cluster of strains was the predominant cluster identified from the outbreaks examined (51%, 47/92), while strains belonging to the NV cluster were implicated in only 5 (5%) of the outbreaks and were not detected for almost a year between June 1996 and April 1997. During each quarter, strains representing at least 3 clusters were detected, and between April and June 1997, at least 1 strain from each of the 6 clusters was detected. During the first quarter of 1996, 83% of outbreaks were caused by strains belonging to the Lordsdale virus cluster, and of these, 65% could be attributed to the common strain. After this peak, the number of outbreaks caused by the common strain steadily fell until the final quarter of the study, when it was detected only once. The number of outbreaks attributed to the Lordsdale virus cluster in general followed a similar pattern as the common strain, peaking during the first quarter of 1996 and steadily declining until the final quarter of 1996, when it was equaled in number by strains of the Toronto virus cluster. During the first 6 months of 1997, no cluster of strains predominated.

Of note, within the limited 18-month period of surveillance, outbreaks appeared to have a winter-spring seasonality, with the number of outbreaks being the greatest in the first quarter of 1996 and 1997. However, outbreaks occurred throughout the year, and September 1996 was the only month in which no outbreaks were reported.

Epidemiologic and laboratory examination of outbreaks. For several outbreaks, results of the sequence analysis provided strong information that either confirmed or disputed the conclusion of the field investigation. We describe four such examples (figure 1).

Outbreak A. Epidemiologists investigating an outbreak (403dade) of gastroenteritis in an elementary school in Miami, Florida, in October 1996, involving 629 students and teachers, also investigated a concurrent outbreak in a nearby day care center (408kind) involving at least 6 children. The spread was linked to ill schoolchildren who had siblings attending the day care center. Although epidemiologists linked the 2 outbreaks, sequence analysis of the implicated NLVs indicated that the strains were unrelated and the outbreaks were independent.

Outbreak B. A cruise ship, which sailed out of Alaska, had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349oman
353hmnc
354wtfd
355cyla
360chor
362cove
367coll
368palm
369vann
370shel
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426nant2
437uavl
LV
uk1-5
438wflu
412winh
429rpri
uk4-19
463lead
uk3-14
uk3-16
sma
403dade
A
416oyob2
SMA
GII
430hccp
457swed
396obdp
mk
434cris

3 outbreaks during a 6-month period in June (387west), October (401wes2), and November (405wes3) of 1996. Investigators were uncertain as to whether these outbreaks were due to onboard transmission of the virus or independent introductions of new strains. Molecular analysis of the polymerase region identified 2 distinct strains, with the strains from the first and third voyages being identical. Further analysis using the larger capsid region differentiated these strains, confirming that they represented independent introductions.

Outbreak C Epidemiologists investigated outbreaks from three successive voyages of a cruise ship, which carried ~1150 passengers and 380 crew members and sailed out of Miami, Florida, during March and April 1997. It was suggested by investigators that a common source of contamination was being harbored aboard the ship. Specimens were available from the first (435roya) and third (442roy2) cruises, and sequence analysis showed identical strains of NLVs from both voyages, which supported the epidemiologists' conclusion that the source of contamination had remained onboard between cruises.

Outbreak D. A small cruise ship had an outbreak of gastroenteritis during a single voyage. The investigating official concluded that this outbreak was caused by a common source of exposure. Sequencing analysis identified two distinct strains (426nant and 426nant2) from the passengers, indicating either multiple sources of contamination or a single source with multiple strains.

Discussion

Our understanding of the etiology of outbreaks of nonbacterial gastroenteritis and the epidemiology of NLVs has increased in parallel with the development of novel, more sensitive, detection methods. A decade ago, when electron microscopy and serologic tests were the only diagnostic methods available, NLVs could be identified in only 20% of these outbreaks, which left open the search for many new etiologic agents [39]. Kaplan and colleagues [40, 41] and Kuritsky et al. [42], examining serologic test results along with clinical and epidemiologic features of patients, suggested that NLVs probably accounted for 45%–50% of these outbreaks in the United States. More recently, Vinje et al. [6], using RT-PCR as the diagnostic tool, attributed 91% of nonbacterial gastroenteritis outbreaks in The Netherlands to NLVs, similar to our own findings using the same methods. These observations underscore our conclusion that NLVs are the most important agents of nonbacterial epidemic gastroenteritis in the United States, responsible for 96% of such outbreaks.

In this study, we applied RT-PCR to the routine screening of fecal and emesis specimens from outbreaks of gastroenteritis. Our ability to detect a virus in 96% of these outbreaks demonstrates the success of this approach and indicates that this method could be used for routine diagnosis of outbreaks in the field. Nonetheless, since only 49% of the specimens examined from these outbreaks were positive, further attention needs to be directed to increasing the sensitivity of the assay by addressing issues such as inhibitors of RT-PCR before this method can be applied to screening individual specimens from sporadic or individual cases of disease. The addition of sequence analysis of RT-PCR products allowed us to monitor the variety of strains and the emergence and disappearance of individual strains over time. The fact that so many genetically different variants are present suggests that the majority of outbreaks were generally unrelated, independent events. By contrast, we observed in some outbreaks the emergence of a common, predominant strain with no obvious epidemiologic link between the outbreaks attributed to it, which occurred in different settings, via unrelated exposures, in distinct age groups, and in distant areas of the country. The sudden emergence and spread of a single strain raises important public health questions about the mode of transmission that permitted the rapid radiation of a single virus. This observation challenges us to explain how it spread to become so predominant and then gradually disappeared.

The usefulness of the molecular data was severely limited by the quality of epidemiologic information available. Our epidemiologic database could identify some descriptive features of public health interest and importance; for example, nursing homes were the most common setting for outbreaks, followed by restaurants or events with catered meals, while transmission was most common via contaminated food or water and person-to-person contact, with great strain diversity between outbreaks. At the same time, more detailed epidemiologic infor-

Figure 1. Phylogram of 86 outbreak strains, 10 reference strains from GenBank, and 15 UK strains [37] based on 81 bases of RNA polymerase gene created using DISTANCES program with Jukes Cantor algorithm, followed by GROWTREE analysis. Eighty-six outbreak sequences reflect 82 outbreaks with single sequences and 2 outbreaks with 2 sequences. For simplification, 4 GI clusters described by Noel et al. [32] were considered as single cluster in this analysis. Snow Mountain agent (SMA) and Melksham virus (MK) appear to form separate clusters on basis of polymerase phylogram, but we have chosen to consider them single cluster based on larger capsid sequence [32]. Insets show outbreak strains that had identical sequence. Arrows indicate outbreaks discussed individually in text, and each letter corresponds to example with same letter. Although 2 strains for example B were identical in polymerase region, further sequence analysis in capsid region distinguished 2 outbreaks, and only 1 sequence is shown in this figure (405wes3) because first outbreak in this example did not qualify for analysis in this study. GenBank accession numbers for reference strains used in this analysis: Camberwell virus (CAV), U46500; Desert Shield virus (DSV), U04469; Hawaii virus (HV), U07611; Lordsdale virus (LV), X86557; MK, X81879; Mexico virus (MV), U22498; Norwalk virus (NV), M87611; SMA, L23831; Southampton virus (SOV), L07418; and Toronto virus (TV), U02030. GV, Gwynedd virus.

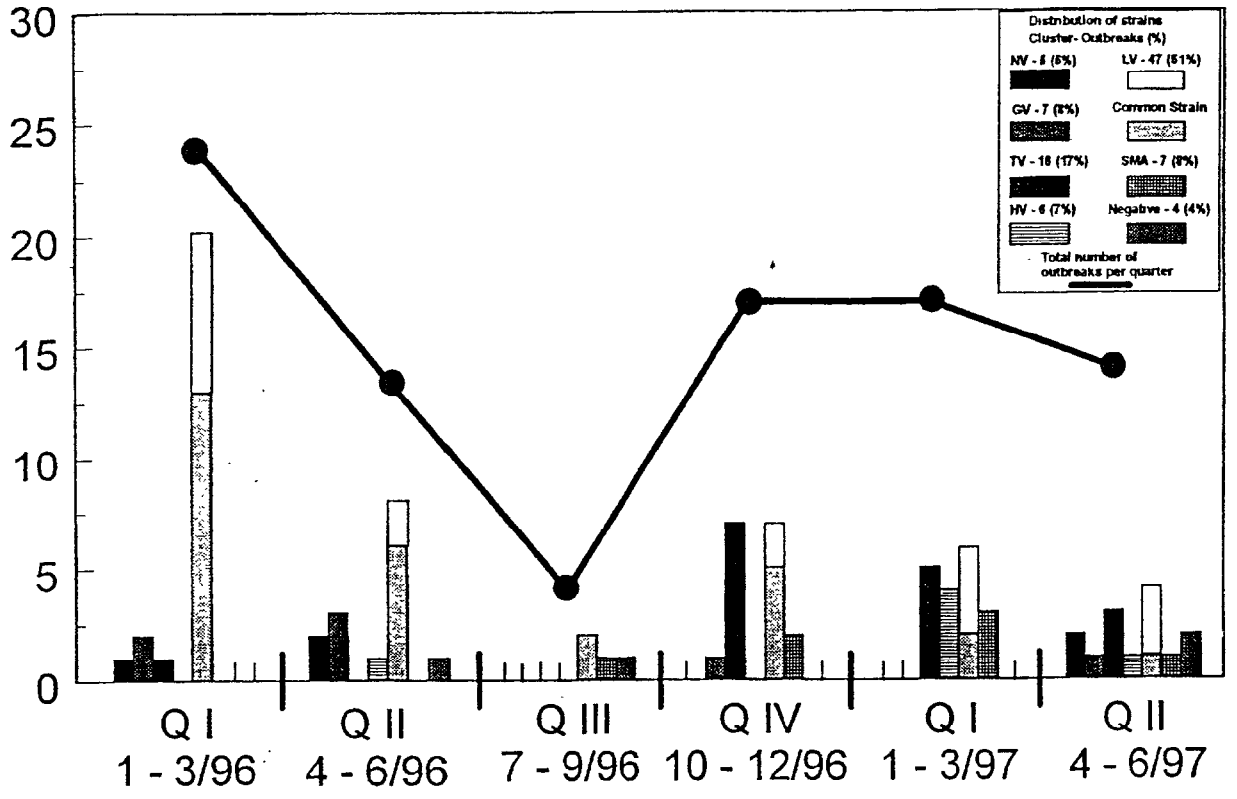

Figure 2. Quarterly distribution of 92 NLV outbreak strains by genetic cluster, January 1996–June 1997. This analysis used 92 outbreaks as denominator rather than 90 because there were 2 outbreaks for which 2 sequences were amplified. We were unable to obtain sequence in polymerase region for 2 additional outbreaks but were able to place these into clusters on basis of sequence from capsid gene, using primers MON381 and MON 383 [32]. Negative outbreaks refer to those that produced negative results with NLV polymerase and capsid primers, as well as being negative for astrovirus, rotavirus, and adenovirus by EIA. Common strain refers to identical Lordsdale-like strain discussed in text. Common strain is represented as subset of Lordsdale cluster (LV) by stacked bar, as it falls into this cluster in phylogenetic analysis. TV, Toronto virus cluster; GV, Gwynedd virus cluster; NV, Norwalk virus cluster; SMA, Snow Mountain virus cluster; HV, Hawaii virus cluster.

mation could aid in determining in a more timely fashion the links between outbreaks or clusters in which a common strain was identified. Our surveillance now relies upon investigations and voluntary reporting by state and local health departments to CDC. The knowledge that these strains might be clustered should encourage more intense and timely future investigations to identify important links between these outbreaks. Prospective determination of unique viruses in multiple outbreaks would allow for rapid efforts to trace the spread of these strains and try to link them to a common vehicle or exposure.

Future studies should focus on furthering our understanding of the epidemiology of the viruses in both epidemic and endemic settings. The availability of new, sensitive detection methods of NLVs not only allows for the detection of virus in more outbreaks but also improves our ability to link outbreaks through the combined efforts of classic epidemiology and molecular analysis. The advances in molecular techniques challenge epidemiologists to identify links between outbreaks caused by the same virus in geographically distinct locations and to explore the modes of transmission that allow the virus to spread rapidly to all areas of the country. Resolution of key epidemiologic questions regarding spread of the virus in outbreaks may lead to new prevention measures to interrupt transmission. While most outbreaks of gastroenteritis can be attributed to NLVs, very little is known about the role of the viruses in sporadic cases. Examination of stool specimens for bacterial pathogens from both hospital inpatients and outpatients has found that no etiologic agent can be determined in 91% of the cases [43]. A future challenge will be to assess the role of NLVs in these cases and to determine if the sporadic cases are linked to outbreaks, but this will require the development of simpler, more sensitive diagnostic methods that can be used in a clinical setting. Improved surveillance of gastroenteritis outbreaks, along with studies examining the role of NLVs in sporadic cases, will

allow for comparisons between mode of transmission, seasonality, and strain types of epidemic and endemic NLV infections. This combination of information will provide a more thorough understanding of NLVs and the illnesses they cause.

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Chemical Disinfection of Medical and Surgical Materials

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The effective use of proper disinfectants and sterilization procedures constitutes a significant factor in preventing nosocomial infections. Physical agents such as moist or dry heat play the dominant role in sterilization procedures in hospitals, and chemical germicides are used primarily for disinfection and antisepsis. In recent years, there has been a virtual explosion in the numbers and types of chemical germicides available to health professionals in the United States. In 1973, the American Society for Microbiology Ad Hoc Committee on Microbiologic Standards of Disinfection in Hospitals surveyed 16 hospitals in various parts of the United States with a combined bed capacity of more than 9000 and found that the average number of different formulations per hospital was 14.5, with a range of 8 to 22. A total of 224 products were used in the 16 hospitals, and 120 of them were proprietary products.

In 1981, the Hospital Infections Program, Centers for Disease Control, Atlanta, Georgia, developed a set of guidelines for the prevention and control of nosocomial infections (CDC, 1981). These guidelines, which will be updated periodically, are provided to all hospitals in the United States. They should be consulted for current information and recommendations for environmental control and prevention of nosocomial infections.

The choice of specific disinfectants in association with protocols for cleaning is a decision that is made broadly and at various levels of hospital and other health care environments. It is evident that no single agent or procedure is adequate for all disinfection or sterilization purposes and that the realistic use of chemical germicides depends on a number of factors that should be considered in choosing among the available procedures. These include the degree of microbial killing required, the nature and composition of the item or device to be treated, and the cost and ease of use of the available agents. This chapter deals with each of these factors and discusses practical methods for evaluating the effectiveness of the various agents and procedures.

CATEGORIES OF MATERIALS

As used in this chapter, the term "medical and surgical materials" includes instruments, equipment, and medical devices, the use of which involves significant risk of transmitting infection to patients or hospital personnel. Consequently, these items should be either sterilized or disinfected to prevent cross-contamination and infection.

The nature of instrument and equipment disinfection can be understood more readily if medical devices, equipment, and surgical materials are divided into three general categories based on the risk of infection involved in their use. These categories were first suggested by Dr. E.H. Spaulding (1972; Spaulding et al., 1977). Although one risks oversimplification in dividing medical devices into such categories, I have elected to retain Dr. Spaulding's clas-

sification system because it is fairly straightforward and logical and has been used for years by epidemiologists and microbiologists when discussing or planning strategies for disinfection and sterilization.

Spaulding believed that strategies for sterilization and disinfection could be better understood and implemented if equipment and items for patient care were categorized by the degree of infection risk involved in their use. He described three categories of such items: critical, semicritical, and noncritical.

Critical items, the first category, are so called because the risk of acquiring infection is great if such an item is contaminated. These are instruments or objects that are introduced directly into the human body—either into the blood or into normally sterile areas of the body. Examples are scalpels, transfer forceps, cardiac catheters, implants, pertinent components of the heart-lung oxygenator, and the blood side of artificial kidneys. The requirement for these items prior to use is sterility, and consequently, one of several accepted sterilization procedures should be chosen.

Items in the second category are classified as semicritical in terms of the degree of risk of infection; examples are flexible fiberoptics, endotracheal and aspirator tubes, bronchoscopes, respiratory therapy equipment, cystoscopes, and urinary catheters. Although these items come in contact with intact mucous membranes, they do not ordinarily penetrate body surfaces. Sterilization of many of these items, although desirable and often more cost-effective if steam autoclaves can be used, is not absolutely essential. Semicritical items should be subjected, at a minimum, to a procedure that can be expected to destroy ordinary vegetative bacteria, most fungal spores, the tubercle bacilli, and small nonlipid viruses. In most cases, meticulous physical cleaning, followed by an appropriate high-level disinfection treatment, gives a reasonable degree of assurance that the items are free of pathogenic microorganisms.

A third category is noncritical items. These do not ordinarily contact the patient directly or, if they do, contact only unbroken skin. Such items include face masks, humidifiers, rebreathing bags, x-ray machines, and a variety of accessory medical and surgical items. Use of these items carries relatively little risk of transmitting infection. Consequently, depending on the particular piece of equipment or item, cleansing with a good detergent in hot water may be sufficient, but with some, the added assurance of chemical disinfection with a low-level disinfectant may be appropriate.

If all medical and surgical materials could be sterilized by steam autoclaving, there would be no need to establish these categories. In reality, however, many such medical devices and articles in everyday use cannot be sterilized by steam autoclaving or irradiation, and chemical germicides must be used. In this context, one must then consider the differences between chemical sterilization and chemical disinfection.

ANTIMICROBIAL EFFECTIVENESS OF CHEMICAL GERMICIDES: DEFINITION OF TERMS

Although the definitions of sterilization, disinfection, and antisepsis (Spaulding, 1972; see also Chapter 44) have been generally accepted, it is common to see all three terms misused, especially by health professionals in hospitals. The exact distinction among the three terms and the basic knowledge of how to achieve and monitor each state are important if long-known principles are to be effectively applied.

Sterilization

Sterilization is defined as the use of a physical or chemical procedure to destroy all microbial life, including highly resistant bacterial endospores. In the hospital, this pertains particularly to those microorganisms that may exist on inanimate objects. Moist heat by steam autoclave, ethylene oxide gas, and dry heat are the major sterilizing agents used in hospitals. As will be seen, however, there are a variety of chemical germicides that have been used for purposes of sterilization and that appear to be effective when used appropriately. These germicides, used in a different manner, actually may be part of a disinfection process. Unfortunately, some health professionals refer to "disinfection" as "sterilization," which leads to a degree of confusion that often becomes magnified with routine use. A good example of this is the use of 2% glutaraldehyde germicides for the disinfection of certain flexible fiberoptic endoscopes. Some practitioners refer to this as "sterilization" of endoscopes. A 2% glutaraldehyde solution is capable of sterili-

zation, but only after extended contact time in the absence of extraneous organic material. Unfortunately, flexible fiberoptic endoscopes are not physically capable of withstanding immersion in fluid for 6 to 10 hours—in fact, most manufacturers recommend that immersion times not exceed 10 minutes. Thus, the procedure the endoscopes are subjected to is one of disinfection and not sterilization, in spite of the fact that colloquially it is referred to in the hospital as "sterilization."

Disinfection

Disinfection is generally a less lethal process than sterilization. It eliminates virtually all recognized pathogenic microorganisms, but not necessarily all microbial forms (e.,g., bacterial endospores), on inanimate objects. As can be seen by this definition, disinfection does not ensure an "overkill," and disinfection processes lack the margin of safety achieved by sterilization procedures. The effectiveness of a disinfection procedure is controlled significantly by a number of factors, each of which may have a pronounced effect on the end results. Among these are the nature and number of contaminating microorganisms (especially the presence of bacterial endospores), the concentration of and length of exposure to the germicide, the amount of organic matter (soil, feces, blood) present, the type and condition of the medical and surgical materials to be disinfected, and the temperature.

Disinfection then is a procedure that reduces the level of microbial contamination, but there is a broad range of activity extending from sterility at one extreme to a minimal reduction in the number of microbial contaminants at the other. It is emphasized that the acceptance of such distinctions is consistent with the ability of a nonsporicidal disinfectant solution to *completely destroy* microbial contamination on medical and surgical materials. Indeed, this probably happens often when spores are absent. Nevertheless, it should not be called sterilization; one would expect that microbiologic assays would be negative only when the item was free of bacterial spores, because of the way it was either used or cleaned or both. This is an important achievement, and consequently there is a need for a term to distinguish between sterilization and the destruction of microbial contamination that is free of bacterial endospores. *Decontamination* is the most appropriate term to be used in this sense, and it implies that items and devices treated as such are rendered safe to handle.

By definition, chemical disinfection differs from sterilization by its lack of sporicidal power. This is an oversimplification of the actual situation, because a few chemical germicides in fact do kill spores, although they may require a high concentration and several hours to do so.

Nonsporicidal disinfectants may differ in their capacity to produce decontamination. Some germicides kill rapidly only the ordinary vegetative forms of bacteria such as staphylococci and streptococci, and some forms of fungi and lipid-containing viruses, whereas others are effective against such relatively resistant organisms as the tubercle bacillus, *Mycobacterium tuberculosis*, other fungi and nonlipid viruses. The latter group therefore represents a level of activity between that of sporicides and many commonly used germicides. Furthermore, absolute sterility is difficult to prove, and as a result, sterility is commonly defined in terms of the probability that a contaminating organism will survive treatment. For example, sterilizing processes are challenged usually with a high number (10^6 to 10^7) of dried bacterial endospores, and sterilization is defined as the state in which the probability of any one spore surviving is 10^{-6} or lower. As pointed out in other chapters in this book, this rationale has been used to establish cycles for steam autoclaves and ethylene oxide gas sterilizers, and it produces a great degree of overkill as well as a quantitative assurance of true sterilization. It is virtually impossible to evaluate liquid chemical disinfection processes by using these criteria, and disinfection procedures cannot be assumed to have the same reliability as sterilization procedures.

Antisepsis

An *antiseptic* is defined as a germicide that is used on skin or living tissue for the purpose of inhibiting or destroying microorganisms. Antiseptics are not discussed in this chapter because they are treated elsewhere in this book, but it should be realized that the distinction between an antiseptic and a disinfectant often is not made. As defined, a disinfectant is a germicide that is used solely to destroy microor-

ganisms on inanimate objects; an antiseptic germicide, however, is one that is used on or in living tissue. Although some specific germicides may be used for both purposes (e.g., alcohols), the adequacy for one purpose does not ensure adequacy for the other. Consequently, it is not good practice to use an antiseptic for the purposes of disinfection and vice versa, because manufacturers specifically formulate germicides for their intended use.

LEVELS OF DISINFECTION

As mentioned previously, Spaulding categorized medical and surgical materials into critical, semicritical, and noncritical items. He also proposed three levels of germicidal action to be recognized for properly carrying out strategies for disinfection in hospitals. The terms "high," "intermediate," and "low" will be used to designate these levels of germicidal action (Table 25–1).

High-Level Disinfection

A number of critical items are damaged by high temperatures, cannot be heat sterilized, and must be disinfected with chemical germicides. As can be seen from Table 25–1, an essential property of a high-level disinfectant is effectiveness against bacterial endospores; usually, if the contact time is long enough, this type of germicide can be used as a sterilant. High-level disinfectants are used often to treat medical and surgical materials, and in the absence of bacterial spores, they are rapidly effective. The absence of spores usually cannot be ensured, although it has been shown that the number of spores on items subjected to such treatments is generally low (Spaulding, 1939). The sporicidal activity of the high-level disinfectant depends on both the specific chemical agent and the manner in which it is used. Table 25–2 shows several disinfectants categorized as having high-level activity. These include aqueous 2% glutaraldehyde, 8% formaldehyde solution in 70% alcohol, 6 to 10% stabilized hydrogen peroxide, and ethylene oxide gas.

In addition, a number of germicides are available commercially that have been approved by the U.S. Environmental Protection Agency (EPA) as sterilants and sporicides. As will be pointed out later, the Association of Official Analytical Chemists (AOAC) sporicidal test is highly stringent, so that chemical germicides designated as sporicides or sterilants by the AOAC are most likely effective. Some of these products combine various chemicals, such as glutaraldehyde with formaldehyde and glutaraldehyde with phenol and phenate. Peracetic acid in liquid and vapor has been described in the past as a high-level disinfectant, but its application presents major difficulties (Portner and Hoffman, 1968; Hoffman and Warshowsky, 1958), especially with medical and surgical items.

Germicides classified as sporicides have been shown to kill large numbers of resistant bacterial endospores under stringent test conditions, but may require as long as 24 hours of contact time to do so (Ortenzio, 1966). Although this type of germicide may qualify technically as a cold sterilant because of the time involved, it may receive little use. In addition, most medical devices in actual practice are not contaminated with extraordinarily high levels of bacterial endospores, so that if a small number of spores comprised the initial population, sterilization may occur much more quickly than 24 hours (Spaulding, 1963, 1972). In other words, given the circumstances of relatively

TABLE 25–1. LEVELS OF GERMICIDAL ACTION

	Bacteria			*Fungi**	*Viruses*	
	Vegetative	*Tubercle bacillus*	*Spores*		*Lipid and medium-size*	*Nonlipid and small*
High	+†	+	+	+	+	+
Intermediate	+	+	–	+	+	+
Low	+	–	–	±	+	–

*Includes usual asexual "spores," but not necessarily chlamydospores and sexual spores.
†Plus signs indicate that a microbicidal effect can be expected when the normal use-concentrations of disinfectants are properly employed.

TABLE 25–2. ACTIVITY LEVELS OF SELECTED GERMICIDES

Class	Use-Concentration of Active Ingredient	Activity Level
GAS		
Ethylene oxide	450-500 mg/L*	High
LIQUID		
Glutaraldehyde, aqueous†	2%	High
Formaldehyde + alcohol	8% + 70%	High
Stabilized hydrogen peroxide	6 to 10%	High
Formaldehyde, aqueous	3 to 8%	High to intermediate
Iodophors‡	30 to 50 mg/L free iodine/ 70 to 150 mg/L available iodine‡	Intermediate
Iodine + alcohol	0.5% + 70%	Intermediate
Chlorine compounds	0.1 to 0.5% free chlorine	Intermediate
Phenolic compounds, aqueous	0.5 to 3%	Intermediate to low
Quaternary ammonium compounds	0.1 to 0.2% aqueous	Low
Mercurial compounds	0.1 to 0.2%	Low

*In autoclave-type equiment at 55° to 60° C.
†There are several proprietary formulations on the U.S. market, i.e., 4% glutaraldehyde and 3% formaldehyde; glutaraldehyde 2% and 7% buffered phenol; and glutaraldehyde 2%, low pH and normal and raised temperatures.
‡See text for a discussion on semantic problems associated with iodophors, available iodine, and free iodine.

few bacterial spores present, sterilization can be achieved by a weaker germicide. Since medical devices and items are not routinely monitored microbiologically, however, one cannot consistently ensure the absence of bacterial spores, so that with certain critical types of medical devices, it may be good practice to rely on those germicides that have been documented in the scientific literature to produce a sporicidal effect in a given amount of time and/or approved by the EPA as sporicides or sterilants.

In any event, these germicides can be relied upon to produce sterility if the exposure elements in terms of contact time, temperature, pH, and other variables are met. A sterilization process accomplished by a chemical germicide gives less assurance than one accomplished by a physical process such as steam autoclaving or dry heat. The latter procedures are much less prone to be affected by human error than those associated with chemical germicides.

One question that is raised consistently is whether high-level germicides should be designated as sterilizing agents. Ethylene oxide, for example, has been widely accepted and officially recognized as a sterilizing agent. In reality, however, its sterilizing capacity varies significantly with the procedures used because ethylene oxide is a chemical disinfectant and is subject to the same factors that influence the antimicrobial efficacy of other germicides. Ethylene oxide sterilization processes performed by large pharmaceutical houses in the United States and elsewhere employ prehumidification, heating, and evacuation of the chamber, and high concentrations of the gas in operating cycles as long as 20 hours. If this process is carried out properly, one can verify sterility as the end result.

Ethylene oxide sterilizers that are commercially available to health care practitioners and that are used in hospitals, medical offices, and other settings display such a wide variation in design and use that ethylene oxide sterilization sometimes cannot be verified. Usually, commercially available large-chamber ethylene oxide sterilizers can consistently sterilize medical items. When these are challenged with high numbers of bacterial endospores (10^6 to 10^8), exposure times of 8 to 12 hours appear to be satisfactory for achieving sterility. This is primarily owing to the sophisticated physical controls regulating temperature, relative humidity, and such prerequisites as prehumidification and evacuation of chambers. Smaller types of sterilizers using ethylene oxide gas are often less reliable in achieving sterility because such critical factors as prehumidification, heating, evacuation, and delivery of ethylene oxide gas under pressure are either absent or inconsistent. With these types of "sterilizers," much more time may be required to achieve sterility, especially when the challenge consists of large

numbers of bacterial spores. If the challenge consists of vegetative bacteria or naturally occurring microbial contamination on in-use medical devices and if the presterilization load of bacterial spores is low, sterility may be achieved, but there is less assurance regarding the effectiveness of the entire process.

The question of how many high-level germicides should be classified as sterilizing agents tends to be academic, because all of them take much longer than a steam autoclave. Although the AOAC sporicidal test is stringent and is a major criterion used by the EPA to designate a germicide as a sterilant, the actual procedures associated with the use of chemical germicides demand much more in the way of microbiologic verification because potency of the chemicals is affected by such factors as organic load, temperature, and contact time. The manufacturer's time and effort spent verifying the effectiveness of the sterilization process, as discussed in other parts of this book, are extensive and technically sophisticated. The same approach cannot be used in a modern hospital. About the best that can be done is, for example, the use of biologic indicators with ethylene oxide sterilizers.

There is no way to verify microbiologically the sterility of medical devices and items that are sterilized without sampling the item itself. The usual procedure is to verify that the germicide can inactivate 10^8 to 10^7 spores of *Bacillus subtilis* or *Clostridium sporogenes*. This can be determined in a laboratory, but variation caused by human error cannot be measured, so that the existence of an established set of procedures associated with the sterilization procedure and the germicide used takes on critical importance. A good example of this is the use of 2% glutaraldehyde germicides, which are capable of sterilization, but only after extended contact time and in the absence of extraneous organic material. Unfortunately, some materials are not physically able to withstand immersion in these fluids for 6 to 10 hours. Even if prolonged contact were possible, the treated materials would have to be rinsed thoroughly with sterile water, dried in a special cabinet with sterile air, and stored in a sterile container to ensure that the materials remain sterile. One can observe staff members in hospitals and other settings, however, soaking items in 2% glutaraldehyde germicides for 10 to 30 minutes, rinsing them in nonsterile water, and referring to the items as "sterile." This particular situation indicates a misunderstanding of the terms "sterile" and "disinfected," as well as overconfidence in a particular germicide and overestimation of the safety of the processed item.

Intermediate-Level Disinfection

Intermediate-level disinfectants do not necessarily kill large numbers of bacterial endospores in a relatively short time, i.e., 6 to 12 hours, but they do inactivate the tubercle bacillus, which is significantly more resistant to aqueous germicides than are ordinary vegetative bacteria. These disinfectants are also effective against fungi (asexual spores but not necessarily dried chlamydospores or sexual spores) as well as lipid and nonlipid medium-size and small viruses. Examples of intermediate-level disinfectants (Table 25–2) include 0.5% iodine, 70 to 90% ethanol and isopropanol, chlorine compounds (free chlorine, i.e., hypochlorous acid as derived from sodium hypochlorite, calcium hypochlorite or gaseous chlorine) at 500 mg/L and some phenolic and iodophor-based disinfectants, depending on formulation.

Although intermediate-level disinfectants are considered effective against viruses, there appear to be some exceptions. Klein and Deforest (1963) have shown that the resistance of viruses to chemical disinfectants varies significantly. They reported that small nonlipid viruses were significantly more resistant to chemical germicides than medium-size viruses with lipid in their protein coats. Some of the most widely used liquid germicides failed to destroy picornaviruses, which include the enterovirus group and the rhinoviruses of the common cold. The point here is that simply because a germicide has good tuberculocidal activity, it cannot be assumed categorically that these germicides are effective against all viruses. Moreover, there are a number of viruses for which tissue culture systems are not yet available and for which documented laboratory testing with various germicides has not yet been accomplished. For example, the human hepatitis viruses (B, and non A/non B) have been difficult to study because they have not yet been cultured in the laboratory. There is no evidence, however, that any of these viruses are unusually resistant to physical or chemical

agents (Miner, 1978). It has been proposed that the resistance level of the hepatitis B virus, for example, is between that of the tubercle bacillus and the bacterial spores, but nearer that of the former (Bond et al., 1977). Since there is a doubt, the most conservative approach would be to use high-level disinfectants for decontamination and disinfection when hepatitis B virus contamination is known or suspected.

Some chemical germicides with good tuberculocidal activity can destroy small nonlipid viruses. As shown by Klein and Deforest (1963), both 70% ethanol and isopropanol are rapidly tuberculocidal (Spaulding, 1964; Heister et al., 1968), whereas only the former was found by Klein and Deforest to destroy the small nonlipid viruses they studied. On the other hand, Wright (1970a) reported that ethanol failed to kill a test virus that, on the basis of Klein and Deforest's study, would be expected to be quite susceptible. At best, an intermediate-level tuberculocide may not necessarily be an intermediate-level virucide.

The germicidal resistance of fungi in general is probably similar to that of gram-positive vegetative bacteria (Prindle and Wright, 1968; Lawrence, 1968). Bacteriostasis may not have been eliminated in many of these reports, however, and there is now reason to believe that some forms of pathogenic fungi may be considerably more resistant than most vegetative bacteria (see Chapter 11). Since it is likely that germicidal chemicals that kill the more resistant fungi may not also be tuberculocidal and virucidal, intermediate-level microbicidal capabilities should be examined with separate classes of microorganisms and referred to specifically.

Low-Level Disinfection

Low-level disinfectants are those that cannot be relied upon to destroy, within a practical period of time, bacterial endospores, the tubercle bacilli, or small nonlipid viruses. These disinfectants may be useful in actual practice because they can kill rapidly vegetative forms of bacteria and fungi as well as medium-size lipid-containing viruses. Examples of low-level disinfectants are quaternary ammonium compounds and mercurials. In addition, the germicidal activity is flexible, depending on the concentration of the active ingredient. Disinfection levels of iodophors and phenolic compounds may be classified as intermediate or low depending on concentrations of the germicide. All germicidal chemicals do not have this capacity. For example, even a 5 to 10% concentration of a quaternary ammonium compound may fail to meet the tuberculocidal or virucidal criterion of intermediate-level disinfection (Klein and Deforest, 1963). A subjective appraisal of commonly used disinfectants is presented in Table 25–3.

SELECTION OF DISINFECTION LEVEL

Patient care equipment and items have been categorized as critical, semicritical, and noncritical, and the level of disinfection that should be used depends in part on the particular category and nature of the item and the manner in which it is to be used.

Critical Items

It would be useless to attempt to name all of the critical items and the large number of medical and surgical materials in use in today's modern hospitals. The concept of a critical item is clear; the user must make his or her own list. All but a few articles in this category are either commercially presterilized or autoclaved by the user. A few important critical items, however, are reused repeatedly and not autoclaved for one reason or another. Examples are the transfer forceps and its jar, an increasing number of plastic parts on medical devices, and hemodialyzers, as well as certain flexible fiberoptic devices. To sterilize these items, one must rely on proper use of certain high-level germicides. Thorough cleansing must always precede chemical disinfection of such items because the mechanical action alone can remove a large proportion of contaminating microorganisms and a good deal of organic material that may tend to inactivate the germicide. The number of bacterial spores is usually small, and they would not be expected to occur in relatively high numbers except when grossly contaminated objects have not been well cleansed; this fact should not be interpreted as a rationale to substitute chemical sterilization for autoclaving. To do so would lower safety standards; also, using high-level germicides is inconvenient because several hours must be allowed to ensure sterilization, and the exposed materials

TABLE 25–3. RELATIVE EFFICACY OF COMMONLY USED DISINFECTANTS*

	Disinfectant	Comment
GAS		
Ethylene oxide	3–4†	Sporicidal, toxic; good penetration. Requires relative humidity of 30% or more. Microbicidal activity varies with apparatus used. Absorbed by porous material. Dry spores highly resistant. Moisture must be present; presoaking most desirable.
LIQUID		
Glutaraldehyde, aqueous	3	Sporicidal, toxic. Active solution unstable.
Stabilized hydrogen peroxide	3	Sporicidal. Use-solution stable up to 6 weeks. Toxic orally and to eyes; mildly toxic to skin. Little inactivation by organic matter.
Formaldehyde + alcohol	3	Sporicidal, toxic, volatile; noxious fumes.
Formaldehyde, aqueous	1–2	Sporicidal, toxic; noxious fumes.
Phenolic compounds	2–3	Stable, corrosive; irritates skin. Little inactivation by organic matter.
Chlorine compounds	1–2	Fast action; inactivation by organic matter. Corrosive; irritates skin.
Alcohol	1	Rapidly microbicidal except for bacterial spores and some viruses. Volatile, flammable. Dries and irritates skin.
Iodine + alcohol	0	Corrosive, rapidly microbicidal, flammable. Causes staining, irritates skin.
Iodophors	1–2	Somewhat unstable, relatively bland, corrosive. Staining temporary.
Quaternary ammonium compounds	1	Bland; inactivated by soap and anionics; absorbed by fabrics. Old or dilute solution can support growth of gram-negative bacteria.
Mercurial compounds	0	Bland; much inactivated by organic matter; weakly bactericidal.

*The values given in this table are my subjective appraisals. More detailed information must be obtained from descriptive brochures, journal articles, and books. Selection of the most appropriate germicide for a particular situation should be made by the responsible personnel in each hospital based upon: (i) whether it is to be used as a disinfectant or an antiseptic; (ii) estimation of the level of antimicrobial action needed; and (iii) the hospital's scope of services, physical facilities, and personnel. Instruments, apparatus, and other objects should be cleansed to remove gross organic soil prior to the use of chemical disinfectants that coagulate protein so as to get good penetration of crevices and porous material. Instruments, as well as rubber and plastic tubing, must be rinsed or flushed with water before coming into contact with skin, and especially mucous membrane, to avoid irritation. For the same reason, aeration is necessary after exposure to ethylene oxide.

†Maximal practical usefulness in the hospital environment is indicated by 4, little or no usefulness by 0.

must be rinsed or aired aseptically and kept sterile before use.

One may debate the importance of an occasional bacterial endospore that may remain viable after a critical item has been disinfected. There have been no epidemiologic studies that can answer this question, but two points deserve mention. First, critical items should receive high-level, instead of intermediate-level, disinfection if this is feasible. Second, for disinfection of semicritical items, the disinfection level should be intermediate, if feasible, rather than low. The second point pertains to the comment that most bacterial spores are nonpathogenic and thus may be ignored without incurring significant risk of infection. The distinction between pathogenic and nonpathogenic species is vague and relative rather than absolute, and in today's hospital environment, the host's level of resistance is the decisive factor in determining whether or not infection will develop. Classic nonpathogens such as *Bacillus subtilis* can produce serious and even fatal infections in immunosuppressed and immunocompromised hosts (Farrer, 1963; Conrad et al., 1971; Tuazon et al., 1979).

Certain critical items deserve special attention. Sterility is essential for hypodermic needles because they enter deep tissues. Use of liquid germicides cannot guarantee sterility because of the narrow lumen. Fortunately, today the widespread use of presterilized disposable needles has almost eliminated the risky practice of reusing chemically sterilized

needles. With the advent of disposable sterile items, there is an increasing practice, based on economic factors, of reusing these items. A good example is the artificial kidney. Hemodialyzers are manufactured and delivered to the user in a sterile state. Assurance that the item is sterile depends on the manufacturer's quality assurance and sterilization cycle verification programs. Fifteen to 18% of the chronic dialysis centers in the United States, as well as some in Europe, reuse these dialyzers (Deane et al., 1978). In spite of the fact that dialyzers can be appropriately cleaned and disinfected, however, they are not subjected to the same stringent sterilization cycles or controls performed by the manufacturer. In this instance, the liability shifts from the manufacturer to the user. So far, this practice appears to be safe if proper cleaning and disinfection procedures are used, but there have been occasions when human error has caused significant side reactions and infections associated with the reuse of dialyzers. In general, reuse of disposable items that are initially sterile is discouraged.

Noncritical Items

Noncritical items consist of a variety of objects and items that offer little risk of transmitting infectious agents. These include face masks, carafes, electrocardiogram electrodes, walls, floors, furniture, and other environmental surfaces that ordinarily do not come into contact with human mucous membranes. Many individuals rely upon hot water or cleansing with detergent in water for these items, but chemical disinfection is also widely practiced, with low-level disinfectants used either alone or in addition to the cleansing.

FACTORS INFLUENCING GERMICIDAL PROCEDURES

Microorganisms vary widely in their responses to physical and chemical stresses. Those most resistant to such stresses are bacterial endospores; few, if any, other microorganisms approach the broad resistance of endospores. A number of factors, some of which are associated with the microorganisms themselves and others with the surrounding physical and chemical environment, influence the antimicrobial efficacy of chemical germicides. Some factors are more important than others, but all of them should be considered when planning strategy for the chemical disinfection of medical and surgical materials.

Nature of the Material

The easiest surface to disinfect chemically is one that is smooth, nonporous, and cleanable, such as a scalpel blade. Crevices, joints, and pores constitute barriers to the penetration of liquid germicides and require prolonged contact times to accomplish disinfection; in fact, it is possible for a disinfection procedure to fail under these circumstances. This is also true of ethylene oxide gas, which has a high degree of penetrability. If microorganisms are entrapped in impervious spaces or within organic materials, the ethylene oxide sterilization procedure may fail, especially when the level of contaminating microorganisms is high and composed of bacterial spores. In the last 10 to 15 years, a number of devices have been made of heat-labile materials that require chemical germicides for sterilization or high-level disinfection. If sterilization is the objective of a treatment, contact times of 6 to 10 hours are required, and this is often detrimental to the material in the devices. For example, flexible fiberoptic endoscopes cannot be subjected to long contact times in liquid germicides without risking the eventual degradation of lenses and other components. It is for this reason that, if sterilization is to be accomplished, ethylene oxide sterilization is the only feasible treatment. Since these instruments are expensive and frequently used, some practitioners have elected to practice high-level disinfection rather than sterilization of these instruments.

The size of a medical device also limits the types of germicides that can be used and governs whether sterilization or high-level disinfection will be the intended treatment. If an instrument is too large to be conveniently immersed in solutions or placed in any ethylene oxide chamber, disinfection may be accomplished by wiping with a liquid. This would include primarily semicritical or noncritical devices.

Thus, the nature and use of a medical device or item may dictate the type and use of a chemical germicide. Practitioners should be aware of this, and when purchasing medical devices, at least one criterion should be the ease with

which the device can be cleaned and sterilized or disinfected.

Number of Microorganisms Present

Under a given set of circumstances, the higher the level of microbial contamination, the longer must be the exposure to the chemical germicide before the entire microbial population is killed. This factor does not stand alone, because the amount of time necessary to inactivate 100 bacterial spores would be significantly longer than the time required to inactivate 100 cells of *Staphylococcus aureus* or most other ordinary vegetative bacteria. When considering a natural microbial population composed of various types of microorganisms that have different degrees of resistance to physical or chemical stress, the survivor curve with all factors controlled would be parabolic and not straight (as it might be if a pure culture of a particular microorganism were used). Furthermore, the most resistant microbial subpopulation, even though it may be present in a fairly lower concentration than the entire microbial population, tends to control sterilization or disinfection time (Bond et al., 1971). A practical illustration of this factor is shown in Table 25–4.

Innate Resistance of Microorganisms

As mentioned previously, microorganisms vary widely in their resistance to chemical germicides, and thus, the types that are present on medical items or surgical materials may have a significant effect on the time as well as the concentration of germicides needed for sterilization or disinfection. The most resistant types of microorganisms are bacterial spores, some of which are significantly more resistant to both chemical and physical stresses (Bond et al., 1970, 1977). In a broad descending order of relative resistance, considerably below that of bacterial endospores are the tubercle bacilli, fungal spores, small or nonlipid viruses, vegetative fungi, medium-size or lipid viruses, and vegetative bacterial cells. Obviously, the biggest difference in resistance is between bacterial spores and vegetative cells. Smaller but important differences exist between the tubercle bacillus and nonacid-fast bacteria and among viruses and fungi. The human hepatitis viruses (B and non A/non B) are difficult to place in this order; it has been estimated (Bond et al., 1977) that their resistance levels are intermediate between bacterial spores and the tubercle bacilli, but more probably toward the latter.

The differences in chemical resistance exhibited by various vegetative bacteria are relatively minor, except for the tubercle bacilli and other nontubercular but acid-fast mycobacteria (Carson et al., 1978), which, presumably because of their hydrophobic cell surfaces, are comparatively resistant to a variety of disinfectants, especially those in the low-level category. Among the ordinary vegetative bacteria, staphylococci and enterococci are somewhat more resistant than most other gram-positive bacteria. It is interesting to note that antibiotic-resistant "hospital" strains of staphylococci do not appear to be more resistant to chemical germicides than ordinary isolates. A number of gram-negative bacteria, such as *Pseudomonas*, *Klebsiella*, *Enterobacter*, and *Serratia*, also may show somewhat greater resistance to some disinfectants than other gram-negative bacteria. This may be significant, because many of these gram-negative bacteria are known to often be responsible for outbreaks of hospital infections, especially in compromised hosts.

Gram-negative water bacteria that have the ability to grow well and achieve levels of 10^3 to 10^7/ml in distilled, deionized, or reverse-osmosis water have been shown to be significantly more resistant to a variety of disinfectants in their "naturally occurring" state (i.e., isolated and grown in pure culture in water without subculturing on laboratory media) as

TABLE 25–4. EFFECT OF NUMBERS ON SPORICIDAL TIME* (Spaulding, 1971)

Spore Count (per blade)	*Test Procedure*	*Positive*	*Negative*
100,000	Dried blood blade	2 hrs	3 hrs
1,000	Dried blood blade	1 hr	2 hrs
10	Dried blood blade	—	30 min

**Bacillus subtilis* spores. Germicides: 8% HCHO-67% isopropanol + 0 5% hexachlorophene.

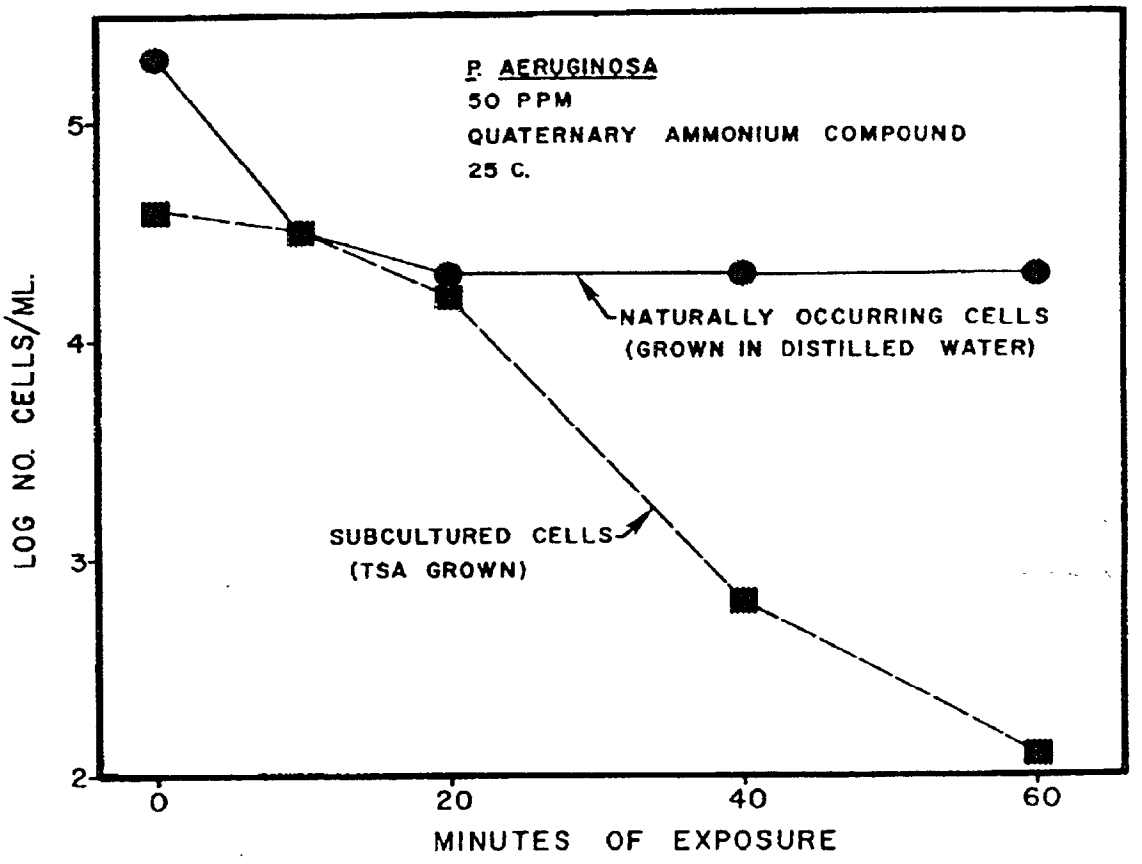

Fig. 25–1. Comparative survival of naturally occurring and subcultured cells of *Pseudomonas aeruginosa* exposed to a quaternary ammonium compound.

compared to bacterial cells subcultured in the normal fashion (Favero et al., 1975; Carson et al., 1972). Figure 25–1 illustrates this phenomenon, which has been shown to occur with nontubercular mycobacteria (Carson et al., 1978). These differences in resistance, although minor, become important when low-level disinfectants are used, particularly at marginal or dilute concentrations, or when disinfectants having greater germicidal properties are used inappropriately (e.g., ingredients used to prepare them are not fresh or significant organic loads are allowed to develop). The resistance of naturally occurring microorganisms also extends to bacterial spores, and it has been shown by Bond et al. (1970) that naturally occurring bacterial spores in soil are significantly more resistant to dry heat than those that are subcultured.

As will be discussed later, it is for these reasons especially that it is not sufficient to design a disinfection procedure solely on data acquired in laboratory tests such as the AOAC use-dilution procedure (AOAC, 1970). It is important also to base such procedures on data collected from actual in-use testing.

Amount of Organic Soil Present

Blood, mucus, or feces, when present on items that one intends to disinfect, may contribute to the failure of a given disinfection or sterilization procedure in two ways. The organic soil may occlude microorganisms and prevent penetration of chemical germicides, or the soil may directly and rapidly inactivate certain germicidal chemicals such as chlorine- and iodine-based disinfectants and quaternary ammonium compounds. This effect is correspondingly greater with weak concentrations and with low-level germicides than with strong concentrations and high-level germicides. In addition,

this factor underscores the necessity and importance of thoroughly cleaning a medical device prior to chemical disinfection. Failure to do this prior to a procedure may cause failure of disinfection or sterilization.

In fact, physical cleaning is quite often the most important step in a disinfection process that, by definition, does not include the "overkill" factor of a sterilization process. Indeed, a report by Webb and Vall-Spinosa (1975) implicated a flexible fiberoptic endoscope in an outbreak of septicemia caused by *Serratia*. This instrument had been "sterilized" with ethylene oxide gas but had not been properly cleaned before the procedure. Consequently, even a rigorous cycle capable of killing exposed bacterial spores may not kill even relatively delicate vegetative bacterial cells if these cells are protected by extraneous organic material. This factor also is intimately associated with the number of microorganisms present, so that effective cleaning procedures that remove organic soil simultaneously tend to lower significantly the general level of microbial contamination associated with the soil.

Type and Concentration of Germicide Used

Generally speaking, with all other variables constant, the higher the concentration of a chemical agent, the greater its effectiveness and the shorter the length of time required to disinfect or sterilize an item. Generally unappreciated, however, are the wide differences in potency that exist among chemical germicides used for the same purpose. For example, Spaulding (1971) compared the tuberculocidal activity of several proprietary phenolic and iodophor-based compounds to that of isopropanol and determined that there were significant differences in the times required for disinfection (Table 25–5).

TABLE 25–5. TUBERCULOCIDAL ACTIVITY OF ALCOHOL PHENOLICS AND AN IODOPHOR

Compound	*Disinfection Times*
Phenolic I, 3%	2 to 3 hrs
Phenolic II, 3%	45 to 60 min
Iodophor, 450 ppm	2 to 3 hrs
Isopropanol, 70% vol	5 min

Simultaneous mucin-loop test. Number of *Mycobacterium tuberculosis* per loop was about 10^4.

Usually the disinfection time can be shortened significantly by increasing the use-concentration. Some chemical germicides are used appropriately only at strong concentrations. This is true for many of the high-level chemical germicides, such as formaldehyde, glutaraldehyde, and ethylene oxide, that are sporicides. It is also true of ethanol and isopropanol, because a dilution with water beyond 60 to 50% would reduce microbicidal activity. Some intermediate-level disinfectants may become useful sporicides when the concentration is increased significantly. This is probably true for hydrogen peroxide, but it is not true for all intermediate-level disinfectants.

In addition, iodine solutions and complexed iodine represent an instance in which confusion has existed with regard to chemistry and strategies of use.

As discussed in Chapter 8 and in the following, iodophor disinfectants are significantly affected by the amount of potassium iodide and water used in their formulation. Consequently, the label instructions describing a particular use-dilution for an iodophor are much more critical than for other chemical germicides because in the case of iodophors, use-dilution is geared to yield the maximum amount of free iodine possible. Under- or overdiluting the disinfectant may significantly reduce its germicidal potency. In other words, if an iodophor disinfectant is meant to be diluted 1:213, an undiluted or 1:10 aqueous dilution may have less microbicidal activity than the use-dilution. Furthermore, it is not clear what iodine species should be used to gauge germicidal potency. Most iodophor disinfectants and antiseptics are formulated to contain a certain amount of complexed iodine yielding a certain percentage of available iodine with usually an unspecified amount of free iodine contained in the use-dilution solution. Available iodine, which is simply the amount of iodine in solution that titrates with sodium thiosulfate, is not microbicidal. Certainly, the amount of available iodine present is important because it can be converted to free iodine depending on a number of other factors, including the amount of water present. Consequently, the manufacturer's instructions for proprietary iodophor preparations should be followed carefully so that the proper use-dilutions of the germicides are

made. In any event, available iodine alone cannot be used to indicate germicidal potency. In fact, Berkelman and co-workers (1981) have shown that a 10% povidone-iodine solution containing 1% of available iodine but 1 ppm of free iodine was intrinsically contaminated with a vegetative bacterium, *Pseudomonas cepacia*.

Duration and Temperature of Exposures

As one might expect, with all other variables constant, the longer the germicidal process is continued, the greater is its effectiveness. An exception would be with some low-level disinfectants for which there might be a minimum threshold of the chemical that may have absolutely no effect on the microbial population. For example, some quaternary ammonium disinfectants used either in insufficient concentrations or in solutions that have deteriorated with age or because of the presence of organic soil not only might fail to affect some microbial populations (especially gram-negative bacteria), but may actually support their growth.

An increase in the temperature of a germicidal solution during the exposure time can significantly increase the efficacy of chemical germicides. One must take care, however, that the temperature does not exceed the point at which the germicide itself degrades, reducing its potency or creating a health hazard by producing toxic fumes. This is especially true with germicidal disinfectants whose active components are halogens or formaldehyde.

COMMONLY USED INSTRUMENT-EQUIPMENT GERMICIDES

As discussed previously, chemical germicides that are classified as disinfectants are, by definition, liquids or gases that are used specifically to inactivate microorganisms on inanimate objects. They are classified usually by activity as high-, intermediate-, or low-level disinfectants. The type of disinfectant that is chosen to accomplish a particular level of disinfection is related primarily to the item being disinfected, and whether that item is critical, semicritical, or noncritical in terms of risk of transmitting infection.

Variables discussed previously, such as the nature of the material, the level of microbial contamination, and the temperature and concentration of disinfectant, are important in the overall disinfection process. Further, in the hospital environment, one of the most critical factors affecting the successful outcome of the disinfection process is the efficiency of the procedure that is used to physically clean an instrument prior to disinfection. Without proper cleaning, most disinfection processes are subject to failure. The chemical germicides discussed in the following are those that are commonly used in hospitals in the United States.

Mercurials

Relatively high concentrations of mercurials are required to achieve significant bactericidal activity. They are fairly low-level disinfectants and have virtually no role in modern disinfection strategies.

Phenolic Compounds

Phenol or carbolic acid is one of the oldest antibacterial agents used in the hospital environment. The parent chemical has been replaced by hundreds of derivative compounds, referred to as phenol derivatives or phenolics. They are considered intermediate- to low-level disinfectants and are used primarily for disinfection purposes in general housekeeping and for noncritical items. The mechanism of action of phenol in high concentrations on the microbial cell appears to be that of a gross protoplasmic poison penetrating and destroying the cell wall and precipitating cellular protein (Prindle, 1968).

In lower concentrations, the eventual death of the bacterial cell appears to be due to inactivation of essential enzyme systems. Phenolics are considered fair to good bactericides in that they are stable and remain active after mild heating and prolonged drying. Subsequent application of moisture to a dry surface previously treated with a phenolic can redissolve the residual chemical so that it again becomes bactericidal. Concentrations of phenolics in the order of 1 to 2% remain active when in contact with organic soil. For this reason, phenolics are among the disinfectants of choice when dealing with gross fecal contamination.

Their usefulness for the disinfection of semicritical items is limited, however, because phenolics as a class are absorbed through porous materials, and the residue may irritate tissue.

Even when disinfected articles can be rinsed thoroughly before use, there is a possibility of residual disinfectant causing tissue irritation. Kahn (1970) reported that equipment and devices so treated caused depigmentation of skin and injury to mucous membranes. Brayman and Songer (1971) pointed out another aspect of phenol toxicity when they found hazardous concentrations in laboratory air near solutions that had been heated up to 45° C (Wysowski et al., 1978). For these reasons and because they are not good sporicides, phenolics are not useful for disinfection of critical and semicritical items. Phenolics have been shown to be effective but rather slow tuberculocides (Table 25–5). Klein and Deforest (1963) reported that 5% phenol killed picornaviruses, but as much as 12% o-phenylphenol did not. On the other hand, Wright (1970b) found several substituted phenolics and cresylic acids to be effective against vesicular stomatitis virus. With the various formulations available in the United States and the lack of published data about efficacy, it is somewhat difficult to suggest uses for phenolics beyond noncritical and a few semicritical items. It is used as a disinfectant for decontamination purposes in laboratories.

Quaternary Ammonium Compounds

A variety of quaternary ammonium compounds, including benzalkonium chloride and cetylpyridinium chloride, have come into fairly wide usage since their introduction as germicides in 1935. As mentioned in Chapter 14, the mode of action of quaternary ammonium compounds appears to be associated with the agent's effect on the cytoplasmic membrane, which controls cell permeability. The quaternary ammonium compounds for many years were the most popular of all classes of disinfectants, primarily because of their blandness and low cost. In the laboratory, they appeared to be germicides with rapid action against test bacteria in vitro, particularly the staphylococci, but under ordinary conditions of use, their germicidal action is somewhat questionable. They are classed as low-level disinfectants with relatively poor activity against gram-negative bacteria. Indeed, commercial preparations containing ammonium acetate have been shown to support the growth of *Pseudomonas* species (Adair et al., 1969). Dixon et al. (1976) have discussed the problems associated with the use of antiseptics and disinfectants based on the quaternary compounds in the hospital environment and have described several outbreaks of disease associated with gram-negative bacterial contamination of quaternary ammonium solutions.

They have no tuberculocidal activity and, because of this, have a role in laboratory procedures for the isolation of tubercle bacilli from clinical materials (Wayne et al., 1962; Smithwick et al., 1975). Indeed, laboratory workers took advantage of the general ineffectiveness of quaternary ammonium compounds against various gram-negative bacteria, including *Pseudomonas* species (especially *P. aeruginosa*), in developing culture media that use quaternary ammonium compounds as selective factors against gram-positive organisms, allowing pseudomonads and some other gram-negative bacteria to grow. Klein and Deforest (1963) found that benzalkonium chloride has no activity against picornaviruses, even in 10% concentration. Because most quaternary ammonium compounds do not acquire intermediate-level activity at any usable concentration, they should not be used to disinfect critical medical items or most semicritical items.

These compounds are rapidly inactivated by contact with protein, cotton fibers, and other organic materials and gram-negative bacteria, such as *Pseudomonas*, Enterobacteriaceae, and *Serratia*, frequently have been noted to grow in them. They are good cleansing agents that can be used effectively for noncritical housekeeping purposes in the hospital and other health care settings.

Chlorine

Inorganic chlorine solutions in concentrations of 0.1 to 0.5% free chlorine are considered intermediate-level disinfectants and are among the best and most convenient germicides for spot disinfection. The mode of action of free chlorine, unlike that of free iodine, is considered to be the inactivation of sulfhydryl enzymes and protein denaturation, as well as inactivation of nucleic acids. Solutions of 1 to 5% (household bleach contains 3 to 5% sodium hypochlorite) are slightly sporicidal and fully tuberculocidal and inactivate vegetative bacteria. Klein and Deforest (1965) reported that all of 25 viruses, including the picornaviruses,

were inactivated in 10 minutes by as little as 0.02% available chlorine.

Free chlorine, as derived from sodium hypochlorite or calcium hypochlorite, has limited use on medical devices in a hospital because of its corrosiveness. It can be used effectively in high concentration, however, as a spot disinfectant or for decontaminating spills, e.g., blood suspected of being positive for hepatitis B virus (Bond et al., 1977). It has been used as a disinfectant for hydrotherapy baths and in hemodialysis systems, but it has the disadvantage of being corrosive. Hypochlorite solutions cannot be left for long periods of time in a dialysis machine. The fact that they must be rinsed from the hemodialysis machine negates their efficacy overall because gram-negative bacteria in the rinsing water tend to grow in these systems in the absence of a disinfectant (Favero et al., 1975; Favero and Petersen, 1977).

Iodophors

Tinctures or iodophors of iodine have been used for many years by health professionals in infection control and for broader control purposes. Iodine (I_2) in its pure form is poorly soluble in water and is saturated at 0.03%, which is 300 ppm free iodine (free iodine being the chemical species I_2). Tinctures of iodine have been used primarily as antiseptic solutions, whereas iodophors are used as both antiseptics and disinfectants. Iodophors are the combination of iodine and a solubilizing agent or carrier in which the resulting complex or combination acts as a reservoir of iodine and liberates small amounts of free iodine when diluted with water. The number of carriers ranges from quaternary ammonium compounds, detergents, and others to polyvinylpyrrolidone (PVP or povidone).

Iodine is believed to function as a general cellular poison and to affect both nucleic acids and proteins. Some iodophors have been marketed as disinfectants and have the disadvantage of being unstable in the presence of hard water, heat, and organic soil, but they appear to be reliable, general-purpose disinfectants if used in concentrations recommended by the manufacturer. Some metallic instruments can be corroded if they are routinely disinfected with iodophors for long periods of time, but nonmetallic items seldom are damaged. Iodophor disinfectants traditionally are classified as low- to intermediate-level disinfectants, depending on concentration. As will be discussed, however, the concentration of the actual microbicidal agent, which is presumably free iodine, is usually unknown.

Formulations of iodophors usually list certain percentages of available iodine that have been used as indicators of germicidal potency. This does not appear to be correct. Many aspects related to the physical and organic chemistry of iodine complexes are not fully understood. For example, a povidone-iodine germicide formulated as an antiseptic usually contains 10% povidone-iodine and is said to yield 1% available iodine. The amount of free iodine present in these solutions has been reported to be approximately 1 ppm (Berkelman et al., 1981; Rodeheaver et al., 1976) and is controlled significantly by the amount of potassium iodide present as well as by the amount of water (see Chapter 8). Concentrated solutions of iodophor contain less free iodine in undiluted solutions than those that are diluted up to a point. Apparently, it is virtually impossible to chemically assay free iodine in the presence of complexed iodine without resorting to an extraction technique using solvents. Thus, one can readily appreciate that the manufacturer's direction for an iodophor disinfectant that calls for a 1:213 aqueous dilution of a concentrated product is designed to give the maximum degree of microbicidal efficiency, which probably correlates with the amount of free iodine present. There appears to be less free iodine in solution, or at least less microbicidal activity, when the product is diluted more or less than the prescribed 1:213 use-dilution.

Available iodine does not appear to be a sufficient indicator of potency for iodophor germicides. Berkelman and colleagues (1981), for example, reported the recovery of *Pseudomonas cepacia* from blood cultures of 52 patients in 4 hospitals in New York City over a 7-month period from April through October, 1980. Epidemiologic investigations indicated that the positive blood cultures were in fact pseudobacteremias, and the source of contamination was a commercially available 10% povidone-iodine solution that was used both as an antiseptic and a disinfectant. It was shown that *P. cepacia* gained entrance to blood culture tubes from povidone-iodine left on the skin prior to venipuncture or from povidone-iodine

that was applied to blood culture bottle tops through which blood was inoculated by syringe into culture media. In addition, *P. cepacia* was isolated directly from the povidone-iodine solutions. This report is not the first to describe intrinsic microbial contamination of commercially available germicide solutions, but one would have thought that these solutions containing 1% available iodine would prevent survival of vegetative bacteria (or bacterial spores).

Unfortunately, most investigators tend to equate available iodine with free iodine. A review of the literature (see Chapter 8; Favero, 1982) concerning microbicidal capabilities of iodophor solutions reveals that virtually no researcher actually reports the amount of free iodine; rather, most express either a dilution of a particular formulation or, more often, amounts of available iodine in mg/L. This confusion may be due to equating the term "available iodine" with the term "available chlorine." The latter is defined as the amount of free (Cl_2 and HOCl) and combined chlorine (i.e., chloramines), both of which are microbicidal, although free chlorine is more active than combined chlorine. The term "available" when used with iodine means the amount that is titratable with sodium thiosulfate; available iodine as such is not microbicidal.

Available iodine can be thought of as an expression of the reservoir of complexed iodine that slowly releases free iodine in a given solution. As the free iodine is depleted, more free iodine instantaneously takes its place. For example, with an iodophor disinfectant that has 1% available iodine and 35 ppm free iodine, the free iodine that is inactivated by reacting with organic materials or bacteria is immediately replaced. Likewise, when it is titrated with sodium thiosulfate, the free iodine concentration is replaced instantaneously from the reservoir of available iodine (even though it is the free iodine that is being titrated); the end result is 1% or 10,000 ppm available iodine. The amount of free iodine, however, is much less, i.e., 35 ppm.

This does not alter the rationale for classifying iodophor disinfectants as intermediate-level disinfectants, but it does present a problem in defining use-concentration. Since it is complicated to assay for free iodine in the presence of iodophor solutions, and since it is current practice for manufacturers to include the amount of available iodine (whether accurate or not) on product labels as an implication of potency, I have elected to retain the use of available iodine as an indicator of potency for denoting strength in Table 25–2, but free iodine levels are listed also. It is emphasized that with iodophors, the manufacturer's directions are much more critical with respect to actual use-dilutions with water than most other disinfectants, and care should be taken to follow label instructions closely.

Alcohols

The value of alcohol as a surgical germicide has been reviewed by Spaulding (1964). Ethyl and isopropyl alcohols are rapidly bactericidal intermediate-level disinfectants and are remarkably active against the tubercle bacillus (Table 25–5). Neither ethanol nor isopropanol are sporicidal, and indeed, both alcohols are sometimes used to store clean spore crops of *Bacillus* and *Clostridium* species. They are fairly effective against all types of vegetative bacteria, but reports on the virucidal properties of alcohol are conflicting (Klein and Deforest, 1963; Wright, 1970a).

Alcohols characteristically evaporate quickly and leave no residue on treated surfaces, which may or may not be an advantage, depending on the item being disinfected. In some instances, they have been known to dissolve the lens mountings of certain types of optical instruments and, upon long exposure, tend to harden and swell plastic tubing, including polyethylene. Further, rubber articles absorb alcohol, and irritation to the skin or mucous membranes may follow. Alcohols in a concentration of 70% by volume may be a good choice for intermediate-level disinfection for some types of semi- and noncritical items.

Formaldehyde

Forty-percent formaldehyde gas dissolved in water constitutes a 100% solution of formalin; 8% formaldehyde in water is 20% formalin. Depending on its concentration, formaldehyde is classified as a high-level (8% formaldehyde plus 70% alcohol) or intermediate- to high-level (3 to 8% formaldehyde in water) disinfectant. Formaldehyde has a broad spectrum of action on microorganisms, and its mode of action is by alkylation with amino and sulfhydryl groups of proteins and ring nitrogen atoms of

purine bases such as guanine (see Chapter 2) (Habeeb and Hiramoto, 1968). Their high sporicidal activities suggest that alkylation of nucleic acids may be more important in microbicidal action than changes in protein constituents. The action of formaldehyde on a protein coat of poliovirus progressively slows down the killing rate by obstructing penetration of the nucleic acid core (Gard, 1959). As mentioned previously, 8% formaldehyde in water is considered an intermediate- to high-level disinfectant; combining 8% formaldehyde in 65 to 70% isopropanol yields a compound that is rapidly bactericidal, tuberculocidal, and sporicidal, but the time required to achieve sterility using high numbers of spores as a challenge may be up to 18 hours or longer, depending on the test conditions (Spaulding, 1966).

Although these solutions of formaldehyde are considered to be intermediate- to high-level germicides, the irritating fumes of formaldehyde limit its usefulness in the hospital environment, and its toxicity for tissue requires that disinfected materials be rinsed thoroughly before use. Since it does not corrode equipment associated with hemodialysis systems, formaldehyde is currently considered the disinfectant of choice in a concentration of 1 to 2% (Favero et al., 1975) and is the germicide most commonly used to disinfect disposable hemodialyzers that are reused. In both instances, however, the problem of residual formaldehyde constitutes a potential health hazard to dialyzing patients, and hemodialysis systems and hemodialyzers must be thoroughly rinsed free of formaldehyde prior to use.

Glutaraldehyde

Glutaraldehyde is a saturated dialdehyde that is chemically related to formaldehyde and has been shown to be two to eight times more sporicidal than formaldehyde (Borick, 1968). Like formaldehyde, glutaraldehyde acts on microorganisms by alkylation, with amino and sulfhydryl groups of proteins and ring nitrogen atoms of purine bases. Disinfectants containing an aqueous solution of 2% glutaraldehyde are considered high-level disinfectants. When exposure times are in the range of 6 to 10 hours at room temperature, depending on the specific formulation, these disinfectants are approved by the EPA as sterilants.

Glutaraldehyde was used for many years as a disinfectant (Boucher, 1972). It was shown that alkaline preparations of glutaraldehyde are sporicidal (Pepper and Chandler, 1963; Borick, 1968). The microbicidal activity of aqueous glutaraldehyde appears to increase at alkaline pH; however, germicidal potency at high pH tends to decrease after storage and use of the disinfectant (Borick, 1968). Acidic preparations of glutaraldehyde can be sporicidal if the temperature is increased to 60° C; and microbicidal activity is increased by ultrasonic energy (Sierra and Boucher, 1971; Boucher, 1974). Other formulations combine glutaraldehyde and formaldehyde, and one is described as a buffered, phenol-glutaraldehyde solution that contains 2% glutaraldehyde and 7% phenol in a phenate buffering system. All of these preparations have been shown to be rapidly sporicidal; the glutaraldehyde-phenate buffering system was reported to be more sporicidal at room temperature than 2% alkaline glutaraldehyde (Pepper, 1980).

Two-percent glutaraldehyde solutions or some of the combinations mentioned previously are classified as high-level disinfectants when used in undiluted forms. These solutions have been approved by the EPA as sporicides and as disinfectants, with recommended contact times at room temperature of 10 to 20 minutes. The actual time in which high-level disinfection is accomplished cannot be based solely on the AOAC use-dilution test. Consequently, recommended times for disinfection will depend on the instrument being disinfected, the type and quantity of the microbiologic load, the amount of organic material and, most importantly, the results of in-use testing with the absence of vegetative bacteria used as a criterion. Most recommended exposure times are in the range of 10 to 30 minutes, and the Center for Disease Control has recently specified a contact time of 30 minutes to accomplish high-level disinfection of inhalation therapy equipment and endoscopic devices (CDC, 1981). Glutaraldehyde disinfectants are not as noxious, irritating to skin, or corrosive to certain types of critical patient care equipment as formaldehyde. Currently, glutaraldehyde-based disinfectants are those used most commonly to disinfect endoscopic equipment.

Hydrogen Peroxide

Hydrogen peroxide has been recognized as a germicide for more than a century. Application

of low concentrations of unstable preparations to tissues containing inactivating levels of catalase, however, led to unfavorable results; this agent has been generally abandoned as an antiseptic. However, it has recently been used in stabilized form. Six-percent stabilized hydrogen peroxide is classified as a high-level disinfectant and has been shown to be sporicidal (see Chapter 11). Hydrogen peroxide has been shown to be bactericidal, virucidal (Mental and Schmidt, 1973), and (in high concentration) sporicidal (Toledo et al., 1971).The latter investigators obtained D values of 0.8 to 7.3 minutes at 24° C with both aerobic and anaerobic spore suspensions by using 10 to 25% hydrogen peroxide. Wardle and Renninger (1975) showed that 10^8 aerobic spores were inactivated at 25° C in 60 minutes with a 10% concentration of hydrogen peroxide. Hydrogen peroxide in concentrations of 3 to 6% appears to constitute a useful class of agents for disinfection of a variety of materials, including medical and surgical devices, and in concentrations of 6 to 25% shows promise as a chemosterilant.

Gaseous Disinfectants

These disinfectants include ethylene oxide, formaldehyde, and beta-propiolactone. All three are toxic to tissues, and because their microbicidal activity is subject to the same kinds of limitations as chemical germicides in general, they should be designated as disinfectants rather than as sterilizing agents. When used appropriately ethylene oxide has been shown to be a practical agent for producing sterility under controlled conditions, and only with ethylene oxide should the process be termed "gas sterilization." Indeed, ethylene oxide is the only one of the three that is used routinely in the United States to accomplish sterilization.

Ethylene oxide is used widely for disinfection and sterilization of instruments and equipment in hospitals and in the pharmaceutical industry. Ethylene oxide, like glutaraldehyde and formaldehyde, accomplishes alkalinization of protein as its mode of action in inactivating microorganisms. Ethylene oxide is considered a high-level disinfectant and, at appropriate concentrations, i.e., 450 to 800 mg/L, exposure times, and humidities, can be used for sterilization of heat-labile articles. A number of commercial devices are available, and this sophisticated equipment is designed to control for the critical variables of prehumidification, temperature, humidity, and ethylene oxide concentration.

Ethylene oxide tends to become absorbed in certain types of materials, and it is necessary to subject exposed materials to a period of deaeration to remove residual ethylene oxide. Since the prehumidification and relative humidity of the gas mixture within commercial gas sterilizers have been shown to be critical, such tolerances virtually negate the use of ethylene oxide in a home-made type of apparatus as was used by some investigators in the 1940s and 1950s. Ethylene oxide gas is toxic, mutagenic, carcinogenic, and irritating to eyes and mucous membranes. Because it is highly penetrating, this gas can leave a residue that must be removed by mechanical ventilation. Ethylene oxide is used routinely in hospitals for the sterilization of heat-labile surgical and medical devices; the effectiveness of the process is usually monitored with biologic indicators as well as physical parameters on the individual sterilizer. Refer to Chapter 2 for a more detailed discussion.

Formaldehyde gas has been used for decontamination and as a disinfectant in formaldehyde chambers. The bactericidal effect is variable, however, and depends significantly on the relative humidity being at 70% or more, which unfortunately promotes corrosion of metals. Formaldehyde fumes are irritating, and the gas penetrates porous materials poorly compared to ethylene oxide. Formaldehyde vapor has been used to sterilize respiratory care equipment, and some techniques have been described by Sykes (1972), who pointed out that sterilization could be achieved in 2 hours by circulation of the vapor through a closed circuit. The formaldehyde gas had to be neutralized with ammonia gas, however, and the machine had to be cycled in a well ventilated room for at least 8 to 24 hours to dissipate all toxic vapors. Because of the time involved and the irritating nature of the gas, this procedure is not used routinely in hospitals in the United States.

Beta-propiolactone has been used as a vapor-phase disinfectant and was found by Hoffman and Warshowsky (1958) to be a more effective sporicide than ethylene oxide. Allen and Murphy (1960) successfully used it for instrument disinfection. Concentration control and side ef-

fects make this gas unsuitable for the disinfection of instruments and equipment on a routine basis in the hospital environment in the United States.

EVALUATION OF ACTUAL GERMICIDAL EFFECTIVENESS

Two basic types of evaluation procedures can be used to compare the microbicidal efficiency of various chemical germicides. First, laboratory tests, using a known number of microorganisms, can be performed to determine (1) the time needed to achieve disinfection for given concentrations of a chemical germicide or a particular procedure, or (2) the concentration of a germicide needed to produce a desired disinfection time. The second type of test involves evaluation of a chemical germicide by an actual or simulated in-use test along with an appropriate microbiologic assay. Depending on the test organisms used, the results can indicate the level of capabilities of a disinfection procedure. Such tests are performed with or without added organic loads.

In the United States, the basic laboratory tests for the evaluation of chemical germicides used by the EPA as well as by scientific investigators have been described by the AOAC (1970). The AOAC use-dilution method involves testing pure cultures of microorganisms that are dried either on surgical threads or in small porcelain cups against a specific chemical germicide at a controlled contact time and temperature, usually 10 minutes at 20° C. It is designed as a dry test (i.e., the inoculum is placed in a receptacle and dried prior to exposure to the germicide). When 10^8 to 10^9 bacterial spores per test vehicle are used, such a test constitutes a fairly stringent challenge. With the dried inoculum, it is fairly difficult for chemical germicides to penetrate to such an extent that the entire population is killed. The assay procedure is based on growth or no growth of surviving microorganisms after exposure of a specific number of carriers. If the test is designed as a sporicidal test, by definition, it involves complete kill of 10^6 to 10^8 dried bacterial spores of *Bacillus subtilis* or *Clostridium sporogenes*. As mentioned previously, this constitutes a severe challenge that could be exceeded only by the use of naturally occurring spores, for example, those in the soil (Bond et al., 1970) or those embedded in dried organic material. Consequently, one can usually be assured that a chemical germicide that has been tested and approved by the EPA for use as a sporicide is an effective chemical sterilant if it is stored and used properly. Obviously, problems associated with misuse or improper preparation (i.e., improper cleaning of an instrument) can contribute to the failure of a sterilization or high-level disinfection procedure.

The AOAC use-dilution test applied to vegetative bacteria is somewhat less reliable. The test as a whole enables the EPA and manufacturers to provide a minimum set of guidelines for comparing and judging the activity of germicidal products. However, this test does not constitute as severe a challenge with vegetative bacteria as it does with bacterial spores. First, the factors influencing microbial resistance to germicides, mentioned in a previous section, are greatly magnified when vegetative bacteria are involved. If the germicide is stored under the wrong conditions or mixed improperly, or if the item to be disinfected is not properly cleaned, the probability is great that the intended level of disinfection, whether it be high, intermediate, or low, will fail to be reached. Furthermore, the number and type of species of bacteria that are used are limited. More importantly, they are pure cultures that have been subcultured for years and maintained in laboratories. That difference in itself will give a false sense of security, because microorganisms in their naturally occurring state tend to be significantly more resistant to physical and chemical stresses than when they are subcultured (Carson et al., 1972, 1978; Favero et al., 1975). Hence, although this test may provide the EPA, manufacturers, and investigators with a somewhat standardized basis for maintaining minimum criteria for comparing germicides, it cannot be used as the sole criterion for selecting chemical germicides to accomplish specific degrees of disinfection, whether it be complete sterilization or high- to low-level disinfection. This is especially true in the hospital environment.

Of great importance in the hospital environment is the manner in which the instrument or item is used, as well as the anticipated risk of disease transmission. In most instances it is not necessary for most hospital laboratories to test the antimicrobial effectiveness of commercial products unless such testing is part of a well designed research or evaluation project. In-

stead, one may rely on the testing performed or validated by the EPA for disinfectant agents. It is a fairly safe assumption that any chemical germicide registered with the EPA meets minimum test criteria. In addition, with certain types of instruments or medical devices, procedures are published in the literature on certain generic chemical germicides, along with suggested contact times (CDC, 1981). There are times, however, when the use of a particular device or item is new or unique, when the intended germicide has not been used previously in a specific manner, or when the germicide is new. In these cases, one may wish to do an in-use test. These tests should be well designed and can be conducted in one of two general ways.

The first type of in-use test is one in which the item is microbiologically assayed after it has been contaminated in actual use and after an appropriate germicidal treatment has been done. The type of microbiologic assay would depend on the intended outcome, i.e., sterilization or disinfection. For example, if the intended disinfectant level for a medical device were high, the microbiologic criterion would be the absence of vegetative bacteria, but not necessarily of bacterial spores. Although this type of testing can be valuable, it is rather cumbersome, and few laboratories have the resources to do this type of testing on a routine basis. It is emphasized that this type of microbiologic testing is designed as part of a research project and should not be incorporated into a program of routine microbiologic monitoring (Favero, 1980).

Another type of in-use test is to operate the medical device or instrument (e.g., a hemodialysis machine) in the laboratory and provide a microbiologic challenge, either by inoculation of naturally occurring microorganisms or with pure cultures, and perform the disinfection procedure. The microbiologic criterion would not change with respect to culture assays, but certain critical variables such as temperature and exact verified germicide concentrations could be controlled.

Regardless of whether one or both types of the in-use tests just described are performed, the contact times invariably are much longer than the 10 minutes employed in the AOAC use-dilution test. For example, most commercially available high-level disinfectants, such as 2% aqueous glutaraldehyde and related germicides, have been approved for disinfection with a contact time of 10 minutes at room temperature. Under actual conditions of use, however, this amount of time may not be sufficient to fully accomplish high-level disinfection, i.e., killing of all contaminating vegetative bacteria, including mycobacteria, but not bacterial endospores. Consequently, contact times of 20 to 30 minutes have been found to be more appropriate (Mackel, 1974; CDC, 1981; APHA, 1978). Several studies (House and Henderson, 1965; Pierce et al., 1970) underscore the need for in-use testing of naturally contaminated equipment to establish more reliable contact times than those achieved with AOAC tests.

It is clear, then, that the actual effectiveness of a chemical germicide is influenced only in part by the nature of the active agent. Of equal and perhaps greater importance is the way in which it is used in the hospital. Many disinfectants, especially the low- and intermediate-level disinfectants, have little margin of safety, and misuse may lead to germicidal failure. Consequently, there is always a tendency for a hospital's infection control personnel to decide to use microbiologic cultures in a limited program to monitor the effectiveness of disinfection and sterilization. It should be emphasized most strongly that routine or widespread environmental culturing is generally discouraged because it offers little data of use to infection control personnel.

Moreover, any environmental monitoring program must be well designed with a specific objective in mind (Favero, 1980). It makes little sense, for example, to evaluate items or areas that are unlikely to play a role in disease transmission. Although floors or furniture and other noncritical items are cleaned and disinfected, they should *not* be tested, even to evaluate the effectiveness of hospital housekeeping personnel; a clean white glove has been said to be a more effective testing tool than a culture plate in these areas. To the extent that it is used, microbiologic monitoring should be limited to high-risk (critical or semicritical) items. Even then, microbiologic monitoring should not take the place of scrupulous attention to the actual performance of the sterilization or disinfection procedures.

STRATEGIES FOR MONITORING CHEMICAL DISINFECTION OF CRITICAL PATIENT CARE EQUIPMENT

Respiratory Therapy and Anesthesia Breathing Circuits

The most important part of an environmental control program to reduce infections transmit-

ted directly or indirectly by respiratory therapy and anesthesia equipment breathing circuits is the use of proper cleaning and disinfection procedures. The most efficient and cost-effective way to accomplish these goals is to sterilize these devices with steam under pressure or ethylene oxide. If this is not possible, the *minimum* procedure that should be used is one that achieves high-level disinfection. In this case, these items may be spot-checked every few months or when disinfection or usage procedures change. Routine or scheduled bacteriologic testing is not required. Although there is no adequate microbiologic guideline for this strategy that is supported by epidemiologic studies, the most widely used criterion of acceptability is the absence of vegetative bacteria on components of the breathing circuits after the disinfection process (Mackel, 1974; APHA, 1978; Favero, 1980).

Hemodialysis Systems

Gram-negative water bacteria can multiply relatively fast in fluids associated with hemodialysis systems such as distilled, softened, deionized, and reverse-osmosis water, as well as in the dialysis fluid itself. Although these fluids do not need to be sterile, excessive levels of gram-negative bacterial contamination pose a risk of pyrogenic reactions and septicemia. A quantitative microbiologic guideline for levels of contamination has been proposed (AAMI, 1974; Favero and Petersen, 1977).

It is suggested that dialysis fluids and water used to prepare dialysis fluids be checked microbiologically at least once a month. Microbiologic guidelines for these procedures include sampling the water used to prepare dialysis fluid at that point at which it is mixed with concentrated dialysis fluid. The level of bacterial contamination should not exceed 200 cells per ml. Dialysis fluid should be sampled at the end of a dialysis treatment, and the level of bacterial contamination should not exceed 2000 cells per ml. In both instances, routine standard plate count or membrane filter assay procedures with appropriate culture media, such as trypticase soy agar or plate count agar, can be used. Hemodialysis systems are among the few medical devices for which periodic microbiologic assays are recommended and for which the few microbiologic quantitative guidelines are actually based on epidemiologic studies (Favero and Petersen, 1977; Favero et al., 1975).

Arterial Pressure Transducers

Arterial pressure transducers have been incriminated in disease transmission, and the best means of control are adequate cleaning and sterilization, as well as proper placement. Scheduled microbiologic sampling is not required, but these items should then be assayed occasionally to determine whether they are being used properly. The criterion of acceptability is sterility.

Endoscopic Equipment

In recent years, a number of flexible and rigid endoscopic devices have been designed for use on patients. These devices have the advantage, in many cases, of eliminating surgical procedures, but since they touch mucous membranes or are placed into normally sterile areas of the body, they are in the category of semicritical to critical items. Preferably, all endoscopes, including flexible fiberoptic endoscopes, should be cleaned appropriately and submitted to a sterilization procedure. There are instances, however, in which either this is not routinely feasible or the state of the art is such that procedures less extensive than sterilization are employed. In these instances, the absolute minimum strategy should be the use of meticulous cleaning and high-level disinfection (Ad Hoc Committee on Infection Control, 1978, 1980; Bond et al., 1979; CDC, 1981). A variety of chemical germicides are classified as high-level disinfectants already have been discussed. When selecting a germicide for use with lensed instruments, however, one must consider not so much the activity of the germicide as the compatibility after extended use with the instrument. Currently, the high-level disinfectants used most widely with endoscopic equipment are ethylene oxide and 2% glutaraldehyde-based germicides. As with other critical and semicritical items, the best way to ensure actual success of the disinfection procedure is to adhere strictly to established cleaning and disinfection protocols. Scheduled microbiologic sampling is not required, but if it is done periodically, the criterion of acceptability is the absence of vegetative bacteria.

Miscellaneous Procedures and Equipment

Numerous items and patient care equipment pose varying degrees of infection risk associated with their use. They may directly contact skin and mucous membranes of body orifices or the peritoneal cavity, but usually not deep tissue. Items in this category, in addition to flexible fiberoptic and endoscope equipment, include hydrotherapy equipment, antiseptic solutions, nonsterile solutions prepared in the hospital, and hemodialyzers. With these items, as with others mentioned previously, the most important element in environmental control is not microbiologic sampling, but rather adherence to tested protocols associated with their cleaning, preparation, disinfection or sterilization, length of use, and maintenance. Even spot-checking these items and procedures is not recommended in most cases because of the absence of meaningful microbiologic guidelines supported by epidemiologic criteria. One arbitrary guideline that can be used is the absence of recognized pathogens after a particular cleansing and disinfection procedure, which can be interpreted, from a realistic standpoint, as the absence of vegetative bacteria.

Unnecessary Microbiologic Assays

There are a number of items and procedures in the hospital and other health care environments for which microbiologic sampling on either a scheduled or periodic basis is neither cost effective nor rational. These include sterile intravenous solutions, injectable solutions, disposable syringes, disposable blood lines, artificial kidneys (even those that are reused), and all other items that are received in a sterile state. Equipment and solutions sterilized within the hospitals need not be sampled microbiologically. Instead, quality assurance testing associated with sterilization procedures, such as appropriate biologic indicator spores (Favero, 1980), should be used to ensure that the sterilization process per se is performing to specifications and that the associated personnel practices are being performed correctly.

It is recognized that inanimate surfaces and air associated with critical areas such as surgical suites and intensive care areas may contain reservoirs of microorganisms. However, the chance for disease transmission in environments that are adequately cleaned and maintained is remote. Environmental control procedures associated with housekeeping and engineering services should adhere to testing cleaning, disinfection, and maintenance protocols. Therefore, microbiologic sampling on either a scheduled or periodic basis should not be done on floors, walls, intramural air, or other inanimate environmental surfaces. Conversely, appropriate sampling should be done when a disease outbreak appears to be associated with a certain part of the environment, such as the air ventilation system (Favero, 1980; CDC, 1981).

Environmental Microbiologic Sampling During Outbreaks of Disease

The strategy that should be used during an outbreak of disease with respect to environmental microbiologic sampling depends on several factors. First, the epidemiologist must determine whether certain procedures, equipment, instruments, or other parts of the environment may be playing a direct or indirect role in the outbreak. An outbreak of nosocomial disease does not mean automatically that environmental microbiologic sampling at any level is required. Second, if environmental microbiologic sampling is believed necessary, the microbiologist and epidemiologist should coordinate the sampling scheme and determine the procedures, items, or parts of the environment that require microbiologic assay.

The application of a microbiologic guideline in this context differs from one that is associated with scheduled or periodic sampling. During the investigation of an outbreak of nosocomial infection, environmental testing is usually directed towards the specific pathogenic microorganism. Consequently, if the outbreak is due to *Pseudomonas aeruginosa*, this organism is sought in the various environmental items that are sampled. In this respect, the guideline tends to be more qualitative than quantitative, although in some instances one must rely on established guidelines. For example, if there is an outbreak of pyrogenic reactions in a hemodialysis center, one would rely on established guidelines (AAMI, 1974; Favero and Petersen, 1977). If water or ice in a hospital is incriminated in an outbreak of nosocomial salmonellosis, assays should be used for determining fecal coliform bacteria, and the total number of microorganisms, in ad-

dition to a selective assay for salmonellae. Thus, the microbiologic guideline here is flexible and basically determined by the nature of the disease outbreak.

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Disinfection, Sterilization, and Preservation

Third Edition

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Viricidal Capability of Resin-Triiodide Demand-Type Disinfectant†

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Polyoma, Newcastle disease virus, and adenovirus, as well as two coliphages, lambda and T4, were inactivated by strong base quaternary ammonium anion-exchange resin-triiodide. Organic matter interfered with viral inactivation capability of the resin-triiodide. The viruses, as they were being inactivated by the resin disinfectant beads, were not retained or filtered by the beads.

A strongly basic quaternary ammonium anion-exchange resin-triiodide (resin-I_3) complex developed in our laboratories proved to be an effective demand-type disinfectant against a wide variety of bacteria (24). The viricidal capability remains in question. Preliminary reports released in 1975 and 1979 (14, 15) tell of viricidal activity, and two papers published in 1980 (16, 21) describe chemical properties of the disinfectant.

Iodine has long been regarded an effective disinfectant (1, 3, 4, 11, 20), but its mechanism of microbial toxicity is obscure. Although iodine in some ways is superior to chlorine (4, 7, 9), it is used only during emergencies (11). Conventional water treatment techniques against virus and amoebic cysts are insufficient (19), and no greater reliability can be expected (11).

Hsu has shown that DNA of *Hemophilus influenza* and RNA of both F2 bacterial virus and tobacco mosaic virus are not affected by iodine, even though the first two organisms have been inactivated (18). Similar results have been reported when the RNA polio virus is used (19). Brammer indicates iodine does not readily react with free nucleic acids (6).

It has been proposed that the bactericidal and viricidal action of iodine involves reaction with protein constituents in either sulfhydryl group oxidation or tyrosyl and histidyl residue substitution (17–19). Iodide ions competitively inhibit substitution (22) but have little effect on oxidation (2). In many cases, acidic conditions reduce viricidal but not bactericidal activity. The triiodide ion in solution has negligible disinfecting ability compared with that of diatomic iodine (2, 10, 18, 26).

† Contribution number 82-103-j, Division of Biology and Department of Chemistry, Kansas Agricultural Experiment Station, Manhattan, KS 66506.

This investigation was designed to determine the efficacy of the resin-I_3 demand-type disinfectant on polyoma, Newcastle disease virus, adenovirus, and bacteriophages lambda and T4.

MATERIALS AND METHODS

Virus and supportive cell lines. A wild-type strain of polyoma virus was grown on primary mouse embryo cells propagated in Eagle medium (13) plus 10% fetal calf serum (FCS) and antibiotics: penicillin, 200 U/ml; streptomycin, 0.2 mg/ml; and kanamycin, 0.01 mg/ml. Polyoma virus stocks, labeled with [*methyl*-^{3}H]thymidine, were prepared, purified, and plaque assayed as described by Consigli et al. (12).

Newcastle disease virus (NDV) was obtained from stock cultures. Primary chick embryo cells were carried in Eagle medium plus 10% FCS. The plaque assay was as described above, except that no second agar overlay was used before neutral red overlaying. The NDV was not labeled.

Human adenovirus type 2 (Ad2) and KB cells (CC117) were also from stocks. The KB cell line was carried in minimal essential medium (13) plus 5% FCS. Adenovirus stocks, labeled with [*methyl*-^{3}H]thymidine, were produced and purified as described by Burlingham and Doerfler (8), with the plaque assay performed by a method described by Rouse et al. (23).

Working stocks of lambda phage (λ)c160 were prepared by infecting nonlysogenic *Escherichia coli* C600, at a multiplicity of infection of 0.2, as the bacterial culture reached 5×10^8 cells per ml in Benzer broth. For labeled λ, [*methyl*-^{3}H]thymidine was added 10 min after phage had been added to form a final concentration of 5 μCi/ml. Purification was by a procedure reported by Bode and Gillin (5), with the plaque assay being performed by the agar layer technique described by Adams (1).

Bacteriophage T4 and *E. coli* NP-4 stocks were on hand. Working stocks were produced by a phage introduction, at a multiplicity of infection of 4, into a growing culture of *E. coli* NP-4 as it reached 10^8 cells per ml in Benzer broth. [*methyl*-^{3}H]thymidine, 2.5 mCi, was added 3 min later with a final concentration of 2.5 μCi/ml. Incubation was at 37°C under constant

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shaking until lysis. Purification was by a method reported by Watson and Maaloe (25), with the plaque assay performed by the agar layer technique described by Adams (1).

Reagents and media. Benzer broth is 1.3% Tryptone (Difco Laboratories) plus 0.7% NaCl. Double distilled water is designated d^2H_2O

Triiodide resin. The procedure for preparation of resin-I_3 is described by Lambert and Fina (U.S. patents 3,817,860 and 3,923,665, 1974 and 1975) and by Taylor et al. (24). The following method of preparation is used currently. Measure 50 meq (we find wet volume measurement best) of a strong base quaternary ammonium anion-exchange resin such as Analytical Grade Dowex 1-X8 20 to 50 mesh (Bio-Rad Laboratories) or IONAC A540 (Matheson, Coleman and Bell). Wash in absolute ethyl alcohol, using five 80- to 100-ml portions. Drain and resuspend in 50 ml of absolute ethyl alcohol containing 5 ml of the methylating agent $(CH_3)_2SO_4$. Permit methylation to continue for 18 to 24 h in a fume hood. Repeat alcohol wash procedure. Follow with five washes, using d^2H_2O, allowing to soak for 30 min per wash. Methylation insures all active sites are quaternary ammonium groups.

To prepare 50 meq of triiodide ion (I_3^-), combine 50 meq each of crystalline I_2 and KI. Dissolve the mixture in a minimum of water, not to exceed 5 ml total. Now add about one-fourth to one-third of the methylated moist resin to I_3^- solution, very slowly. Initially, care must be taken to add only resin and interstitial water. Subsequently, the remaining resin can be added more quickly, but excess water must be avoided until the very end. Allow this slurry to stand overnight. The resin will become black-brown, and the supernatant will become nearly colorless. Any aliquot of this prepared resin may be used to make up columns of various sizes. The 50 meq of resin-I_3 has a 37-ml wet volume and a 13 ± 1-ml void volume. Resin-I_3, under the trade name "Triocide" or "Pentacide," can be purchased from Water Technologies Inc., Ann Arbor, Mich.

Experimental procedures. *Purified polyoma virus* stocks, 2×10^9 PFU/ml, were serially diluted with d^2H_2O to approximately 100 PFU/ml. Beginning with the highest dilutions, 20-ml viral suspensions were passed through 50 meq of Ionac A 540 resin-I_3 at 30 ml/min. A 20-ml d^2H_2O wash was passed between each dilution to flush the column. Plaque assays were performed on each eluate. To observe the effects of d^2H_2O on polyoma, two d^2H_2O dilutions were prepared. One was held at room temperature during the experiment, and the other was held in an ice bath for 24 h.

To examine the effects of organic matter, stocks of [*methyl*-^{3}H]thymidine-labeled polyoma (10^8 PFU/ml) in Eagle medium plus 10% FCS were diluted 1:10 in d^2H_2O. Aliquots (5 ml) containing 6,000 μg of organic matter per ml were passed through 50 meq of Ionac A 540 resin-I_3 and untreated resin at 30 ml/min. That was followed with a 15-ml d^2H_2O wash. A total of 20 ml of eluate was collected for PFU determination, and radioactivity was determined by liquid scintillation counting (LSC).

Stock suspensions of 10^6 PFU of unlabeled Newcastle disease virus per ml, in Eagle medium plus 10% FCS, were diluted 100-fold with d^2H_2O, resulting in 600 μg of organic matter per ml and 2×10^4 PFU per ml. This suspension of NDV was passed through a 50-meq Ionac A 540 resin-I_3 at 31 ml/min. Aliquots of 10-fold dilutions in d^2H_2O were held at 25°C for the experimental duration and in an ice bath for 7 days. PFU determinations of test and controls, including suspensions held in d^2H_2O at two temperatures, were on chick embryo tissue culture.

Ionac A 540 resin-I_3 eluate was used to prepare Eagle medium plus 10% FCS in which mouse embryo tissue culture was grown and to prepare medium 199 used to grow primary rabbit kidney tissue. All cell monolayers were incubated at 37°C with 5% CO_2 and observed for plaque development.

Purified [*methyl*-^{3}H]thymidine-labeled Ad2, 5.4×10^9 PFU/ml, was serially diluted with d^2H_2O to produce suspensions containing approximately 10^4 through 10^5 PFU/ml. Dilutions, beginning with the lowest number of PFU per milliliter, were passed through 1.0 meq of Dowex 1-X8 resin-I_3 at 7 ml/min. Twenty-five milliliter washes, with d^2H_2O between dilutions, were discarded. Eluates were plaque assayed. Additionally, to determine whether there was adsorption to Dowex 1-X8 resin-I_3, a suspension of 10^8 PFU with radioactive counts of 10^2 cpm/ml was passed through a 1-meq column. A total of 25 ml, in 5-ml increments, was collected. Radioactivity was tested by LSC. PFUs were not determined.

Purified λ stocks, labeled with [*methyl*-^{3}H]thymidine and containing 10^{12} PFU/ml, were serially diluted to approximately 7×10^4 to 7×10^7 PFU/ml in 1-liter portions of d^2H_2O. Half of each 1,000 ml of diluent, 500 ml, was passed through a 50-meq Dowex 1-X8 resin-I_3 column, and 500 ml was passed through an untreated 50-meq Dowex 1-X8 resin column at 80 ml/min. The lowest PFU concentrations were passed first with 200-ml flushes of d^2H_2O in between. The washes were discarded. Eluates of each dilution (50-ml) were collected in individual flasks. Phage dilutions passed through untreated control resin were similarly collected. Plaque assays were performed immediately. In addition, 1-liter volumes of [*methyl*-^{3}H]thymidine-labeled λ, 10^8 PFU/ml in d^2H_2O with about 10^2 cpm/ml, were each passed through a 50-meq Dowex 1-X8 resin-I_3 and a 50-meq untreated control Dowex 1-X8 resin column at 80 ml/min. Samples for LSC were collected at various eluate volumes only for retention differentiation, not for PFU determination. As with Ad2, the 10^8 PFU/ml was 10 times more concentrated than the column could handle effectively.

TABLE 1. *Various concentrations of polyoma virus inactivated after passing through a 50-meq Ionac A 540 resin-I_3 column*[a]

Concn (PFU/ml)		Reduction (%)
Before passage	After passage	
1.4×10^7	2×10^3	99.99
1.2×10^6	0	100
1.5×10^5	0	100
5×10^4	0	100
3×10^2	0	100

[a] Polyoma suspended in d^2H_2O was stable for more than 2 h at 25°C or 24 h in a crushed-ice bath.

TABLE 2. Effect of organic matter[a] on 50 meq of iodinated and noniodinated Ionac A 540 resin in columns

Resin	Concn (cpm/ml)		Recovery (%)	Concn (PFU/ml)		Reduction (%)
	Before passage	After passage		Before passage	After passage	
Iodinated	6.23×10^4	4.83×10^4	77.5	1.9×10^7	2.8×10^6	85
Noniodinated	6.26×10^4	5.07×10^4	80.9	2.7×10^7	1.5×10^7	45

[a] Influent contained [*methyl*-^{3}H]thymidine-labeled polyoma virus suspended in Eagle medium diluted 1:10 in d^2H_2O

Stocks of T4 labeled with [*methyl*-^{3}H]thymidine were serially diluted with d^2H_2O. Three pH values (5.5, 6.0, and 7.0) and two concentrations (10^5 and 10^7 PFU/ml) were prepared. These suspensions were passed through a 50-meq treated Dowex 1-X8 resin-I_3 column at 80 ml/min. Samples were taken for LSC and plaque assay before and after resin passage.

RESULTS

Table 1 shows the results of polyoma passage through 50-meq Ionac A 540 resin-I_3. Surviving polyoma viruses did not appear until 10^7 PFU/ml had been applied. Loss of virus was not due to the effects of d^2H_2O.

The results of passing polyoma virus in 1:10 Eagle medium plus 10% FCS (6,000 μg of organic matter per ml) through Ionac A 540 resins are shown in Table 2. Radioactivity yields of 77 and 80% and decreased inactivation efficiency are illustrated.

NDV, with initial counts of 2×10^4 PFU/ml, when passed through a 50-meq Ionac A 540 resin-I_3 column, was completely inactivated. The d^2H_2O dilutions were stable for 2 h at room temperature: 5×10^5 at the start and 6×10^5 after 2 h; they were only slightly decreased after 7 days in an ice bath.

No harmful effects of cellular growth characteristics on tissue culture were noted when Ionac A 540 resin-I_3-eluted d^2H_2O was used in the culture preparation. Cell monolayers and plaquing were unchanged in all cases.

Passage of Ad2 dilutions through Dowex 1-X8 resins yielded the results shown in Table 3. Survivors did not appear until 10^5 PFU/ml were passed through 1 meq of Dowex 1-X8 resin-I_3. In labeled virus column adsorption trials, nearly 100% of the counts applied were recovered. No binding was observed.

The effectiveness of a Dowex 1-X8 resin-I_3 50-meq column against λ phage closely followed results derived in previous experiments. No survivors appeared until 10^6 PFU/ml were passed, and less than 0.01% survived at 7×10^7 PFU/ml (Table 4).

In the experiment in which 1 liter of [*methyl*-^{3}H]thymidine-labeled λ (10^8 PFU/ml) was used, initial radioactive counts were 330 to 350 cpm/ml and remained constant on passage through treated and untreated Dowex 1-X8 columns.

The results with T4 were the same as those with the λ phage (Table 5). Additionally, inactivation at pH 5.5, 6.0, and 7.0 was complete in treated Dowex 1-X8 columns until suspensions of 10^7 PFU/ml were used. Radioactive ^{3}H-tracer indicated no adsorption on any Dowex 1-X8 resin-I_3 columns. Initial counts were 1.52×10^3 cpm/ml, and after passage through resin-I_3, eluate counts remained unchanged.

DISCUSSION

The results demonstrate the ability of the quaternary ammonium anion-exchange resin-I_3 disinfectant to inactivate three animal viruses and two coliphages under the conditions stated. To this list can be added inactivation of type 1 *L* Scab polio virus at 3×10^6 PFU/ml (H. F. Maassab, University of Michigan, Ann Arbor, personal communication).

To minimize the effect of anions in tap water, suspensions were made in double-distilled water. Anions and alkaline pH tend to favor column disinfecting action by releasing iodine (15). Our published reports (12, 15, 24; J. L. Lambert

TABLE 3. Adenovirus type 2 inactivated after passing through Dowex 1-X8 resin-I_3 and nontreated columns

PFU/ml (nontreated column)	PFU/ml (resin-I_3 column)	Reduction (%)
4.4×10^4	1	99.99+
4.9×10^3	0	100
6.7×10^2	0	100
5.2×10^1	0	100
6	0	100

TABLE 4. Inactivated λ phage, labeled with [*methyl*-^{3}H]thymidine, after passing through 1 meq of Dowex 1-X8 resin-I_3

Initial PFU/ml	Survivors (PFU/ml)	Reduction (%)
7.3×10^7	910	99.99+
7.0×10^6	40	99.99+
6.9×10^5	0	100
6.7×10^4	0	100

TABLE 5. Inactivated T4 phage, labeled with [*methyl*-^{3}H]thymidine, after passing through column containing 50 meq of Dowex 1-X8 resin-I_3[a]

Initial PFU/ml	pH	Survivors (PFU/ml)	Reduction (%)
7.56×10^7	7.0	TNTC (not $> 5 \times 10^3$)	99.99+
7.56×10^7	5.5	2.64×10^1	99.99+
1.7×10^5	7.0	0	100
4.0×10^5	6.0	0	100
1.7×10^5	5.5	0	100

[a] No radioactivity was adsorbed to any of the resin-I_3 columns. TNTC, Too numerous to count.

and L. R. Fina, U.S. patent 3,817,860, 1974) suggest that elemental iodine is transferred to bacteria (or virus) on contact with resin-I_3 beads in a column. The method of iodine transfer to microbes and the complex action of iodine biological inactivation are under study. The resin-I_3 does not appear, in the case of Dowex 1-X8 resin, to filter out virus (polyoma). Organic matter competed for resin-I_3 active sites and inhibited virus inactivation, as was expected. It is of interest that organic matter at levels of 600 μg/ml will allow the inactivation of 2×10^4 NDV PFU/ml. From these experiments, it is possible to speculate that the resin-I_3 is most efficacious when the water to be made germfree is low in organic matter.

Work in progress, and in manuscript, examines further resin-I_3 use with public health in mind. To be reported are physical properties of resin-I_3 and iodine inactivation of bacteria and virus.

It should be noted that the viruses used do not best represent waterborne types. We simply use those on hand and thus established a state-of-the-art base for future studies.

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EPIDEMIC VIRAL ENTERITIS IN A LONG-STAY CHILDREN'S WARD

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Summary Two outbreaks of acute gastroenteritis occurred in 1974 in a long-stay children's ward. Electron microscopy demonstrated rotaviruses in fæces from the affected children in the first outbreak, and adenoviruses in fæces from affected children and a nurse in the second outbreak. The illness in both outbreaks was very mild; but the diarrhœa associated with rotavirus infection usually lasted 5–8 days (in one patient it lasted for 28 days) and sometimes started with vomiting; whereas the adenovirus-associated diarrhœa lasted only 2–4 days and was not associated with vomiting. Neither the rotaviruses nor the adenoviruses could be established in tissue-culture.

Introduction

ACUTE enteritis of young children associated with rotaviruses [1] (orbivirus-like particles) in the fæces has lately been described.[2–4] In all studies a disease of considerable severity was reported, associated with pronounced dehydration requiring urgent parenteral therapy in a high proportion of children studied; one group [4] reported seven deaths. All the reports describe patients sent to hospital because of severe diarrhœa. This paper describes an outbreak of acute diarrhœa, associated with rotaviruses, of very mild character in a long-stay children's ward. In contrast, a second outbreak of diarrhœa in the same ward was associated, not with rotaviruses, but with adenoviruses. Electron microscopy of fæces was of great value in investigating both outbreaks.

Patients and Location

In the first 4 months of 1974 there were two outbreaks of acute infectious diarrhœa among children in a ward of an orthopædic hospital. The patients were 3 months to 3 years of age; most were receiving treatment for congenital dislocation of the hip. In the main body of the ward there are fifteen cots arranged in three rows; on each of two opposite sides are five cubicles which open on to the main ward through sliding doors.

The sluice consists of a large glazed earthenware sink with a central drain down which the contents of pots and napkins are washed. Both the sink and the surfaces around it are routinely wiped down with disinfectant after use.

Preliminary microbiology.—Salmonellæ, shigellæ, and enteropathogenic strains of *Escherichia coli* were not found in either outbreak. Rotaviruses were seen by direct electron microscopy in the fæces from affected children in the first outbreak and adenoviruses were seen in fæces collected during the second outbreak.

First Outbreak (Rotaviruses)

Between Jan. 27 and the first week of March, 1974, six of twenty-six children in the ward were affected by enteritis.

Clinical course.—Three of six children vomited on the first day of illness and one of these vomited on 2 consecutive days. Frank diarrhœa persisted for 2–15 days, except in one child in whom it continued for 28 days. This was followed in four children by "loose stools" rather than "green diarrhœa" for an additional 5–10 days. Fever was not typical; only one child was mildly pyrexial (37·2°C), and only on 1 day. No child was severely affected and no intravenous therapy was required. The orthopædic surgeon in charge wrote in the notes of one child "This virus is purely academic", and operated on the child's hip the next day; recovery was uneventful. Virological investigation did benefit one child who had been on a gluten-free diet because of suspected cœliac disease. When a normal diet was tried diarrhœa developed. But as rotaviruses were found, the normal diet was continued and in a few days the diarrhœa ceased without the patient having to return to a special diet. The incubation period was probably as short as 2 days, at least for one patient. Diarrhœa developed on the day of admission in the first case, who had presumably become infected elsewhere. She was moved to another cubicle; in another child, admitted to the vacated cubicle and cot on the same day, loose stools developed 2 days later and frank diarrhœa after 3 more days. Diarrhœa developed after another 7 days in a third child, and after another 11 days in a fourth child (but within 5 days of admission to the ward). Two other children became ill 8 and 10 days after the first case.

Duration of virus excretion.—Samples of fæces were collected from all children in the ward; rotaviruses were found only in fæces from children with loose stools or diarrhœa. Stools from two children without diarrhœa contained other viruses—in one case poliovirus type 2 and in the other Coxsackie virus type B5. Rotaviruses were found in stools up to 23 days after the onset of symptoms in one child whose diarrhœa did not clear up for another 10 days. Virus could no longer be found in fæces from two other patients 9 and 15 days after onset.

Antibody studies.—Sera taken during the acute stage of the infection and at times which varied from several days to several weeks later (determined by the patients' operation date) were examined by immunoelectron microscopy.

Sera collected 3–8 days after onset of symptoms contained antibody, as demonstrated by antibody fibres attached to the virus particles and agglutination of the particles. Evidence for a later increase in antibody levels came from the observation that sera collected during late convalescence also agglutinated the virus, but the virus particles were then so heavily invested with antibody that their outlines were obscured.

Human rotaviruses are serologically and morphologically very similar to those causing calf diarrhœa.[1] When sera taken during the acute stage of infection were tested by an immunofluorescence method, using calf-kidney cells infected with calf-diarrhœa virus [5] as the antigen, brilliant fluorescent staining was obtained.

Second Outbreak (Adenoviruses)

Acute diarrhœa developed in six of nineteen children and a nurse in the same ward between April 27 and 29, 1974.

Clinical course.—Vomiting was not a symptom. Diarrhœa persisted in the children for 24–48 hours, but they were not otherwise ill. One child had a temperature of 37·1°C, but the others were afebrile. The nurse went off sick on the 3rd day of her illness and remained away for the rest of that week. Unlike the first outbreak, which had

continued for several weeks, this outbreak lasted for only 3 days and there were no secondary cases.

Virology.—Adenovirus-like particles were found in fæces from four of the six children affected and from the nurse, but not from any of the other thirteen children. Salmonellæ, shigellæ, and enteropathic strains of *E. coli* were not found. Despite continuous efforts over several months in the Birmingham and Shrewsbury laboratories, and more recently in the Central Public Health Laboratory at Colindale, all attempts, using a wide variety of tissue-cultures, failed to isolate the adenoviruses from the fæces. Feeble cytopathic effects were seen in some HEp2 cultures after 10–20 days' incubation, but virus could not be sub-cultured from them. The adenoviruses in clarified faecal suspensions were much more strongly agglutinated by anti-sera to adenovirus type 7 than by antisera to other types. Luton[6] found this method of typing to be reliable. The result was surprising because adenovirus type 7 was not regarded as a difficult virus to isolate, and we ourselves had never found it to be so.

Discussion

In 50 to 60% of cases of acute diarrhœa in young children, rotaviruses can be seen in the fæces.[1-4] No rotaviruses were seen in our second outbreak; one child had previously had rotavirus diarrhœa in the first outbreak and was known to have antibodies to that virus. In the first outbreak rotaviruses were only seen in children with diarrhœa or "loose stools"; virus excretion did not continue after diarrhœa ceased. Carriers or sub-clinical cases were not found—in contrast to enteroviruses which commonly produce symptom-free infection.

Electron microscopy of fæces enabled us to discover the adenoviruses quickly and to assign a provisional serotype to them, although we could not establish them in tissue-culture.

In the first outbreak one child seems to have brought the virus into the ward and transmitted it to others either directly or indirectly. The very similar virus of calf diarrhœa retains full infectivity in fæces kept for 7 months at room temperature.[7] It is reasonable to expect that the human virus will also be stable, and that it may persist in the environment unless destroyed by careful disinfection. In the second outbreak, adenoviruses seem to have come from a common unknown source and to have affected several children at the same time.

We thank Sister E. J. Greasley and Sister B. Sakuntanaga for their help in investigating these outbreaks; the Shrewsbury public-health laboratory staff and Mr R. E. Hadley for technical help; and Dr M. G. Pereira and Dr P. G. Higgins for their attempts to isolate the adenoviruses.

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NEW APPROACH TO MANAGEMENT OF INTRACRANIAL ANEURYSMS*

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Summary In six cases an attempt was made to relieve the tension on intracranial aneurysms by temporarily clamping the internal carotid artery in the neck, so as to increase the expansibility of the artery. This approach was based on the concept (or "A principle") that hæmorrhage is caused by the aneurysm having to bear the full force of systolic pulse pressure when atherosclerosis prevents this pressure being taken up by the normally expansile arterial wall. Follow-up has been fairly short, but the preliminary findings in four of the six patients are encouraging. More attention must be paid in the future to the significance of atherosclerosis in the onset of bleeding from intracranial aneurysms and the incidence of postoperative problems. The argument that atherosclerosis permits the transmission of the systolic pulse directly to the aneurysm wall requires further investigation. The earlier pathological signs of atherosclerosis must receive greater attention, and post-mortem study of the walls of arteries in immediate juxtaposition to aneurysms with high-powered magnification is required.

Introduction

THE high mortality and morbidity which follow both conservative and surgical treatment of patients with intracranial aneurysms have led to attempts to take a new look at the problems of causation and therapy. One difficulty with the argument that intracranial aneurysms arise from congenital lesions is that the considerable majority "bleed" only after the age of 40. One explanation for this is the onset of atherosclerosis. In the early life of arteries, the systolic impulse in arterial walls is seen and felt as an expansion of the wall; the pulse has its systolic component. The pulse wave (i.e., the expansion of the wall) travels along the artery rather like the peristaltic wave in the œsophagus and gut but from a different cause, the heart in systole. When the artery is affected by atherosclerosis its wall becomes less elastic, so that when the systolic pulse wave travels to the periphery the blood-flow pressure is transmitted directly to the periphery and is not taken up by the expansion of the arterial wall. Because intracranial aneurysms lie at the fork junction of two branches of the artery, the blood-flow pressure in systole is transmitted more or less directly to the mouth of the aneurysm. Therefore, whereas previous to the onset of atherosclerosis each systolic wave of pressure was absorbed by the expansion of the arterial wall and the arterial blood-flow pressure at the periphery was less, now, with hardening of the arterial wall in atherosclerosis, each systolic wave of pressure is transmitted directly to the aneurysm, its contents, and wall.

On this model (or "A principle") atherosclerosis

* Based on a paper read at a meeting of the Academy of American Neurosurgeons and the Society of British Neurological Surgeons, held in Bermuda on Nov. 7, 1974.

Chapter 28

The Special Problems of Nosocomial Infection in the Pediatric Patient

E. Lee Ford-Jones, M.D.

THE MAGNITUDE OF THE PROBLEM

At the Sixth Northern Pediatric Congress Meeting in Stockholm, Sweden in 1934, data were presented indicating that as many as 50% hospitalized patients acquired cross-infections, with small infants and patients with tuberculosis and diabetes being especially susceptible (1). A review of records of the Infants' and Children's Hospitals, Boston, in 1935 and 1936 indicated that 12.6% of 1455 infants admitted to hospital had febrile disturbances appearing sufficiently long after hospitalization to justify the assumption that they had been acquired in the hospital (1). With measles, chickenpox, German measles, polio, diphtheria and pertussis present in only 2.6% of patients being admitted, nosocomial contagious disease occurred only rarely, and the appearance of such contagious diseases led to such radical temporary improvement in the technique used in the ward that cross-infection was reduced. No nosocomial gastroenteritis occurred, but admissions for diarrhea were unusual (0.6%). Of all children remaining in the wards longer than 2 weeks, 26.6% acquired infections, accounting for 90% of all hospital infections. Others at the time identified the need for closed cubicles with outside exhaust for measles and varicella cases (1). Masks, confinement of each infant to a separate cubicle, exclusion of visitors, control of nurses' health, administration of cold vaccine to nurses, and employment of older nurses who would not be predisposed to catarrhal infection were recommended (1, 2). While the risk attributable to hospitalization was not known, it was hoped that control measures found effective in hospital would be of use in public health control. In a prospective review of 26 pediatric wards in 14 British hospitals in 1949, cross-infection was documented in 7.1% of patients during the hospital stay. Most common were acute respiratory infections (38%) and gastroenteritis (21%) (3).

Recent data on the problem of nosocomial infections in pediatric patients indicate that the problem is still with us. In general, the magnitude of the problem in pediatric hospitals remains poorly defined. There are few systematic reviews, and much information is based on reports of outbreaks of disease. Nosocomial infection rates between 2.3 and 12.6/100 admissions or discharges have been reported (1, 4–15) and are listed in Table 28.1. Lower rates of nosocomial infection were found in the National Nosocomial Infection Surveillance study (16) and varied depending on the type of hospital surveyed, as shown in Table 28.2. In general, surveillance methods varied widely, as did diagnostic criteria. For example, intravenous catheter-related infections were not always clearly defined (4), colonization was included in some studies (11, 13), positive wound cultures were required for a diagnosis of wound infection (11), and incubation periods for presumptive diagnoses of infectious respiratory and gastrointestinal infections have varied (4, 6). Noninfectious complications of hospitalization were included in one report (1).

Table 28.3 includes infection rates by service reported in the literature (4, 10, 13–15). The major problem areas have included the intensive care nursery and pediatric intensive care unit, neurosurgery, cardiovascular surgery, and oncology services (4, 10). These are all areas with severely compromised patients with prolonged stays undergoing many diagnostic and therapeutic interventions.

Infection rates in different anatomic sites vary widely (Table 28.4) (1, 4, 5, 10, 12, 13). The most comprehensive report to date (4) and the only

Table 28.1. Overall Nos

Hospital
Children's Hospital of Buffalo
University of Virginia Hospital (5)
Strong Memorial Hospital (6–9)
Children's Hospital Medical Center (10)
Adelaide Children's Hospital (11)
Universityof Kentucky Hospital (12)
The Hospital for Sick Children, Toronto (13–15)
Infants' and Children's Hospitals, Boston (1)

Table 28.2. Infection R

Type of Hospital
Nonteaching
Small teaching
Large teaching

* UTI, urinary tract infec
BACT, bacteremia.

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tract infections accounte
tinal infections 16.8%, b
tract, surgical wound, s
about 8% of all nosoco
adults, gastrointestinal
problem in children and
are not.

Table 28.1. Overall Nosocomial Infection Rates Reported in the Literature

Hospital	Year Reported	No. of Pediatric Beds	Infection Rate/100 Patients	Primary Method of Surveillance	Duration of Surveillance
Children's Hospital of Buffalo	1984	181	4.1	Review of nursing Kardex. All lab reports. Medical record discharges.	12 months
University of Virginia Hospital (5)	1981	Unknown	4.7	Review of nursing Kardex weekly to select high risk patients for chart survery	70 months
Strong Memorial Hospital (6–9)	1980	Unknown	2.3	Ward visits twice weekly. Viral lab reports.	17 months
Children's Hospital Medical Center (10)	1972	343	4.6	Ward visits to head nurses twice weekly. Bacteriology lab reports.	12 months
Adelaide Children's Hospital (11)	1970	Unknown	2.8	Ward visits to ward nurses thrice weekly. All lab reports.	33 months
Universityof Kentucky Hospital (12)	1967	Unknown	5.3	Review of mycology and bacteriology lab reports.	57 days
The Hospital for Sick Children, Toronto (13–15)	1962	609	6.5	Daily ward visits.	12 months
Infants' and Children's Hospitals, Boston (1)	1938	Unknown	12.6	Chart review.	24 months

Table 28.2. Infection Rates/100 Discharges by Site on Pediatric Services NNIS 1980 to 1982 (16)

Type of Hospital	Nosocomial Infection Rate at Different Sites of Infection*						
	UTI	SWI	LRI	CUT	BACT	Other	All Sites
Nonteaching	0.04	0.06	0.04	0.06	0.01	0.07	0.27
Small teaching	0.22	0.08	0.21	0.15	0.19	0.45	1.3
Large teaching	0.24	0.16	0.23	0.20	0.18	0.44	1.45

* UTI, urinary tract infection; SWI, surgical wound infection; LRI, lower respiratory infection; CUT, cutaneous; BACT, bacteremia.

one to include viral disease found that respiratory tract infections accounted for 23.9%, gastrointestinal infections 16.8%, blood 10.0%, and urinary tract, surgical wound, skin, and eye, each for about 8% of all nosocomial infections. Unlike adults, gastrointestinal infections are a major problem in children and urinary tract infections are not.

Risk Factors

Age. The attack rates were highest on infant wards (6.7%), lowest among adolescents (1.6%) and intermediate on wards housing toddlers and school-aged children (3.4% and 4.1%) (4). Others have found the infection rate during the first year of life to be twice that of subsequent age groups

Table 28.3. Overall Nosocomial Infection Rate by Service Reported in the Literature

Hospital	Nosocomial Infection Rate per 100 Admissions or Discharges												
	Intensive Care Nursery	Nursery	Pediatric ICU	Medical	Surgical	General Surgery	Neuro-surgery	Cardio-vascular	Ortho-paedic	Neurol-ogy	Tumor Therapy	Ear-Nose-Throat	Dental
Children's Hospital of Buffalo (4)	22.2	1.7	11.0	4.9	2.0	3.7	17.7	11.2					
Children's Hospital Medical Center (10)				4.2		4.2	18.6	4.7	3.9	1.0	21.4	0	0
The Hospital for Sick Children (13–15)				4.4	10.3								

(10), and a decrease in infection rates after the first 10 years of life has been reported by others (13–15). At a teaching hospital in Lagos, the 0 to 4 age group had the highest number of infections (17). A very low risk of 10 infections/1000 discharges during the first decade has been reported, but this study did not provide details of the population and surveillance methods (18).

Other host risk factors and length of stay have generally not been addressed (19), except for some viral respiratory disease in which the risk appears to be most related to the duration of hospitalization, with 45% of the infants hospitalized for 1 week or more becoming infected and the proportion continuing to increase with the length of hospitalization (20).

The Special Problem of Viral Disease

Viral pathogens are a major cause of nosocomial disease in pediatric patients. In a report comparing the relative importance of bacterial and viral pathogens, *Staphylococcus aureus* was identified as the most common pathogen, followed by rotavirus (4). Viruses—including rotavirus, respiratory syncytial virus, parainfluenza, adenovirus, echoviruses, coronavirus, calicivirus, and astrovirus—caused more infections than gram-negative bacilli. Respiratory infections of known etiology were more commonly caused by viruses than bacteria. All enteric infections were caused by viruses. In summary, viral agents caused 14.3% of all nosocomial infections and probably many more of the respiratory and enteric infections from which no infectious agent was recovered.

During 17 months of surveillance for viral infections at the Strong Memorial Hospital, the pediatric service had the highest rate of nosocomial viral infection, approximately 5-fold higher than that on the adult medical service (6). Viral infections occurred at a rate of 72.4/10,000 pediatric admissions, accounting for 35.4% of all nosocomial infections. Unlike adults in whom exogenous and endogenous viral infections (i.e., herpes simplex virus, cytomegalovirus varicella-zoster) were equally common, the pediatric infections were caused almost exclusively by RSV, adenovirus, and parainfluenza virus. In a review of new episodes of fever occurring in hospitalized children, one-third were associated with the recovery of respiratory viruses (21). Other presumptive cases of viral disease were reported during hospital-wide surveys and included 75 cases of measles, 25 cases of varicella, 5 cases of rubella,

Table 28.4. Proportio

Hospital
Children's Hospital of Buffalo (4)*
Univerity of Virginia Hospital (5)
Children's Hospital Medical Center, Boston (10)
University of Kentucky Hospital (12)
The Hospital for Sick Children, Toronto (13)
Infants' and Children's Hospital, Boston (1)

* Only center to incluc

2 cases of mumps, and (10, 11, 13).

Most reports of nc diseases have been in outbreaks. Rates of in tients have not been dren at home or in da or fatal disease from a munity virus such as attributed to hospitali sons, it would seem pr of occurrence of these defer them to an olde

1. the severity of F age (23) with syn ring on re-expos ratory viruses thi particularly seve 25).
2. Wheezing in as may be attributa
3. Intestinal infecti a normal host o tional status is a important deter (30) and can l diarrhea in the adapted to fastir
4. Infants with oti are at high risk f effusion (32).
5. Both epidemiol evidence suppo

Table 28.4. Proportional Distribution of Nosocomial Infections by Site of Infection

Hospital	Respiratory Tract (%)	Gastro-intestinal Tract (%)	Blood (%)	Urinary Tract (%)	Surgical Wound (%)	Skin (%)	Eye (%)	Miscellaneous (%)
Children's Hospital of Buffalo (4)*	23.9	16.8	10.0	8.9	8.4	8.0	7.9	16 0
University of Virginia Hospital (5)	8.4		22 7	14.1	0.36			54.5
Children's Hospital Medical Center, Boston (10)	17.0	3.2	13.6	17.2	26.0	10.6		9.1
University of Kentucky Hospital (12)	35			5	30			30
The Hospital for Sick Children, Toronto (13)	41.8	20.0			13.5			24.7
Infants' and Children's Hospital, Boston (1)	59.8	0				15.6		

* Only center to include viral infections systematically.

2 cases of mumps, and 1 coxsackie B encephalitis (10, 11, 13).

Most reports of nosocomial viral infectious diseases have been investigations of recognized outbreaks. Rates of infection in hospitalized patients have not been compared to those in children at home or in day care facilities, but severe or fatal disease from a relatively uncommon community virus such as adenovirus 7 (22) has been attributed to hospitalization; and for several reasons, it would seem prudent to minimize the risk of occurrence of these infections and endeavor to defer them to an older age:

1. the severity of RSV is inversely related to age (23) with symptomatic infections occurring on re-exposure to this and other respiratory viruses throughout life. Infectious are particularly severe until 3 years of age (23–25).
2. Wheezing in as many as 10% of children may be attributable to bronchiolitis (26–29).
3. Intestinal infections occurring frequently in a normal host or in a patient whose nutritional status is already marginal can be an important determinant of nutritional health (30) and can lead to chronic intractable diarrhea in the young infant who is poorly adapted to fasting (31).
4. Infants with otitis media in early infancy are at high risk for chronic otitis media with effusion (32).
5. Both epidemiologic data and experimental evidence support the hypothesis that primary viral infection increases host susceptibility to secondary bacterial, fungal, and protozoal infection (33).

Efforts should be made to protect hospitalized children, particularly those less than 2 years of age, from these extra infections which may have serious sequelae.

Hall has identified a number of principles of nosocomial viral infections which distinguish them from bacterial infections (34):

1. They reflect the pattern of activity in the community rather than hospital bacterial flora;
2. The incidence, age of person affected, type of illness, and seasonal occurrence are typical of infection with that virus in the community;
3. They are constantly being introduced into the hospital since some children may be silently or asymptomatically shedding virus;
4. They may occur in any patient rather than just in high risk patients.

The incidence of nosocomial viral infections has probably been grossly underestimated for the following reasons: viral diagnostic services are not readily available; patients have not been followed after discharge (most cases of nosocomial varicella have been identified only after discharge (35, 36); asymptomatic infection is common; multiple or sequential infections may occur, and the necessary repeat cultures are not obtained; and infections are so common as to be considered "the norm." Additional studies are needed using

Table 28.5. Criteria for Nosocomial Viral Infection*

Virus	No. of Days from Onset of Illness
Respiratory	
Influenza	3
Respiratory syncytial	5
Parainfluenza	5
Adenovirus	7
Rhinovirus	3
Gastrointestinal	
Norwalk-like	2
Rotavirus	3
Exanthematous	
Measles	10
Mumps	18
Rubella	18
Roseola	10
Chickenpox	13
Picornavirus	
Echovirus	5
Coxsackievirus	5
Poliovirus	4–30
Hepatitis	
A	15–45
B	60–180
Non-A, non-B	18–89
Herpesvirus	
Herpes simplex	3
Herpes zoster	3
Cytomegalovirus	3
Viral respiratory illness (not cultured)	3

*From Valenti WM, Hall CB, Douglas RG, Menegus MA, Pincus PH: Nosocomial viral infections. 1. Epidemiology and significance. *Infect Control* 1:33–37, 1980.

standard diagnostic criteria such as those set forth by the Centers for Disease Control (CDC) with the appropriate modifications for viruses such as those seen in Table 28.5. Laboratory-based surveillance, including a review of all patients with positive viral cultures, a 4-fold rise in viral antibody titer between acute and convalescent sera, or a positive test for rotavirus by counterimmunoelectrophoresis, may be the most sensitive method of surveillance. This method detected 75% of infections as compared to 25% detection using ward visits by the infection control nurse (6).

Postoperative Wound Infections

Postoperative wound infections account for between 0.36 and 30% of nosocomial infections in pediatric patients (4, 5, 10, 12, 13) (Table 28.4). The highest proportion of wound infections is found in centers which have not included viral causes of nosocomial infections. One center has noted that wound infections constitute less than one-half of the infections acquired by surgical patients with the exception of the orthopaedic service, although infections following cutdown and procedures other than classical surgery were included in this report (10).

The frequency of postoperative wound infection at the Milwaukee Children's Hospital varied slightly by service, with an overall clean wound infection rate of 3.1% (37). Patients were followed for 1 month by questionnaire at the physician's office. Between 21% and 53% of wound infections in adults may go unrecorded because they appear after discharge (38). Children requiring simple day surgery procedures, which are generally clean, low risk surgery, were excluded from analysis, leaving perhaps a higher risk group to account for higher infection rates than those seen in adults. Twenty-five years ago, The Hospital for Sick Children in Toronto reported wound infection in 2.1% of patients undergoing clean surgery and 3.1% of patients following any surgical procedure (14). Higher rates have been reported by others (39), as shown in Table 28.6.

The subject of prophylactic antibiotics in children has recently been reviewed (40–43). There are virtually no studies documenting the efficacy of perioperative antibiotic prophylaxis of wound infection in children, although the principles should be the same in children as in adults (44), and the evidence of inappropriate use appears similar (37, 45, 46). Prophylactic antibiotics were given to 50% of patients undergoing clean surgery and continued for 4 days or more in about half of cases (37). Of antimicrobial agents used on surgical services at a large pediatric teaching hospital, 66% were considered inappropriate with respect to drug, dose, timing, duration, or indication (45). In another study, antibiotics were prescribed for 62% of children who had surgery, and prophylaxis, largely inappropriate, was the sole reason for antibiotic use in 73% of the patients (46). Retrospective case-control studies (47–52) on the value of shunt prophylaxis have demonstrated efficacy, but randomized controlled trials (53–56) to date, all with inadequate sample size, have not agreed as to the benefit of such prophylaxis. Infection following ventriculoperitoneal shunt surgery may ultimately have a negative effect on the child's intellectual function (57).

Two epidemics related to streptococcal carriage

Table 28.6. Number o Wounds

Reference	
37	2
39	

in pediatric surgeons 59). Anal carriage of found in one orthopae on three of four patier infections following ort *Streptococcus equismil* isolated from two p wound infections perfc within a 3-day period. from which *S. equism* colonization of the nos

Bloodstre

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Endemi

The etiology of bac defined to date. Bloo for between 10 and 2 mial infections. In a r emia from the Johns 1974, the attack rate infants under 1 year (61). In 1984, Buffa reported that 42% wer *epidermidis*, reflectin populations and new i cause serious infecti percent were caused b month study, *Escher* tococci, *Pseudomon* counted for the rem which were polymic cases of nosocomial tients in intensive ca 10-fold higher in the those in nonintensiv ciation with hyperali of patients, and in nosocomial bloodstr ated with the use of ir eters, although the st

Table 28.6. Number of Postoperative Wound Infections (%) by Classification of the Surgical Wounds

Reference	Wound Class				
	Clean	Clean-Contaminated	Contaminated	Dirty	Total
37	26 (3.1)	11 (7.8)	4 (17)	3 (10)	44 (4.2)
39	7 (3.5)	8 (16)	30 (37)		45 (13.6)

in pediatric surgeons have been described (58, 59). Anal carriage of group A streptococci was found in one orthopaedic surgeon who operated on three of four patients who developed wound infections following orthopaedic procedures (58). *Streptococcus equismilis* (Lancefield group C) was isolated from two postoperative orthopaedic wound infections performed by another surgeon within a 3-day period. He had perianal dermatitis from which *S. equismilis* was isolated, as well as colonization of the nose and rectum (59).

Bloodstream Infections

This subject is extensively reviewed in Chapter 19, and the problem in pediatric patients appears to differ very little from that in adults, although the amount of blood collected is often small, and there may therefore be some concern about the sensitivity of the test (60).

Endemic Infections

The etiology of bacteremias has been poorly defined to date. Bloodstream infections account for between 10 and 23% (4, 5, 10) of all nosocomial infections. In a report of nosocomial bacteremia from the Johns Hopkins Hospital, 1968 to 1974, the attack rate was 1.90/1000 patients for infants under 1 year of age excluding newborns (61). In 1984, Buffalo Children's Hospital (4) reported that 42% were caused by *Staphylococcus epidermidis*, reflecting trends observed in other populations and new information on its ability to cause serious infections (62–71). Twenty-four percent were caused by *S. aureus*. During the 12-month study, *Escherichia coli*, *Klebsiella*, streptococci, *Pseudomonas* and *Candida sp.* accounted for the remainder of infections, 13 of which were polymicrobial. Sixty percent of all cases of nosocomial bacteremia occurred in patients in intensive care areas (4) with attack rates 10-fold higher in these areas (2.8 and 2.1) than those in nonintensive care areas (0.2). An association with hyperalimentation was noted in 37% of patients, and in total 83% of all cases of nosocomial bloodstream infections were associated with the use of indwelling intravascular catheters, although the strength of this association is not clear because the population from which the infected patients came was not described. At Children's Hospital, Boston in 1972, *E. coli* and *Klebsiella-Enterobacter* were the most common isolates; *S. epidermidis* was dismissed as a contaminant at that time except when associated with intravenous polyethylene catheters (10).

Device-Related and Epidemic Infections

There are few data on colonization of pediatric catheters (72, 73). The definition of an episode of bacteremia in the patient with an intravascular device which is not removed is controversial. If it is unclear whether a patient's Broviac catheter is the source of sepsis, quantitative bacteriologic techniques may be more sensitive and specific (74). In all nine positive catheter samples in one study of pediatric patients, the concentration of pathogens in cultures obtained through the catheter was 10 times as great as that observed in the peripheral venous sample. In two patients with septicemia not attributable to the catheter, quantitative cultures yielded low colony counts in the catheter sample. This method detected pathogens within 16 hours and identified infections with multiple organisms. Surveillance cultures taken through a Broviac catheter were not helpful in detecting impending septicemia.

In a report of patients with polymicrobial bacteremia, an intravascular device could be implicated in seven patients with polymicrobial bacteremia and in two patients with combined monomicrobial pseudobacteremia (75). Septic thrombophlebitis has been described following Teflon catheter insertion (*Klebsiella pneumoniae*, *S. epidermidis*) and venous cutdown (*Pseudomonas aeruginosa*) (76, 77). Subperiosteal abscess has also been described (77). Heparin locks have been used safely in cystic fibrosis patients (78). Prolonged use of lines for patients receiving total parenteral nutrition and chemotherapy has been associated with an infection rate of 2.68/1000 catheter use days (79). In some cases of central line infection, the infection may be adequately treated with antibiotics and without removal of the line (79, 80). Results of urokinase therapy have been variable (81,82).

Epidemic bacteremia in pediatric patients has been associated with contaminated infusion fluids including 5% dextrose in 0.2% sodium chloride to which potassium chloride had been added in the hospital's central pharmacy (*Enterobacter*) (83), heavily contaminated tops of intravenous bottles (*Enterobacter cloacae* and *Enterobacter agglomerans*) (84, 85), stored nonbacteriostatic saline used in a diagnostic tracer procedure (*Achromobacter xylosoxidans*) (86), and arterial pressure monitoring devices (*Pseudomonas maltophilia*) (87).

General host risk factors for nosocomial bacteremia include malnutrition (88) and age (89, 90), with the attack rate being highest in infants. Immunosupression is discussed in a subsequent section of this chapter. Nosocomial bacteremia with either one or more organisms may also be the result of Munchausen syndrome (91) or a child abuse variant, Munchausen syndrome by Proxy or Polle Syndrome (92, 93). One infant developed two episodes of bacteremia in hospital: one due to *P. aeruginosa* and the other due to *P. cepacia*. *Citrobacter freundii*, and *Klebsiella oxytoca* acquired when the mother used her husband's insulin syringes to inject contaminated water into the child's intravenous tubing (92). Another 4 ½-year-old child presented with "immunodeficiency disease" before the diagnosis of Polle syndrome was made (93, 94).

Respiratory Therapy

While this subject is dealt with in detail in Chapter 20, two points are worthy of emphasis. Aerosol therapy via croupettes is probably of little if any benefit in conditions characterized by pathology in the smaller airways, such as pneumonia and bronchiolitis. Of the mass of droplets produced by either the jet or ultrasonic nebulizer, (80 to 90%) are removed by the nose or oropharynx with nasal or normal mouth breathing (95). The possible benefits of a few milliliters of water in the lower respiratory tract should be weighed against the well known hazards of infection (96–98), uneven thermal environment, and the probable adverse psychological impact of therapy in most patients, and unnecessary use should be avoided.

Because of the minimal temperature decrease over the length of the Bain circuit in pediatric patients, humidifier temperatures must be kept significantly lower (i.e., 36.9 ± 1.9°C) than the recommended 50°C to avoid excessive airway temperature and thermal injury (99, 100). In a study of 14 pediatric patients ventilated for 99 days, 21.9% of cascade humidifier cultures and 46% of inspiratory tubing cultures were culture-positive (99), an incidence of colonization much lower than that found in Craven et al in an adult population (101). None of the patients exposed to this contaminated respiratory equipment developed respiratory disease as a result of therapy, although two became colonized with the same organism. *Acinetobacter calcoaceticus* was recovered from the cascade water in quantities of 10 to 20 organisms/ml (99).

Urinary Tract Infections

Although nosocomial urinary tract infections may account for between 5 and 17.2% of nosocomial infections in pediatric hospitals (4, 5, 10, 12), their true importance is difficult to assess because of the frequency of asymptomatic infections in nonhospitalized patients (1 to 2% of healthy school-age girls (102)) and the need for sterile urethral catheterization or bladder aspiration to obtain an uncontaminated urine in infants and young children. In healthy adolescent females undergoing spinal fusion, a statistically significant relationship between the number of straight catheterizations, the number of hours of urinary retention/stasis, and the subsequent development of urinary tract infections has been identified (103). Clean intermittent catheterization appears to be a safer and more effective means of regular bladder emptying than ileal loop diversion in the pediatric patient (104, 105).

Eye Infections

A recent cluster of 10 nosocomial eye infections in pediatric and adult patients resulting in blindness in three patients was traced to bacterial dispersion during tracheal suctioning (106). Only the left eye was infected in 9 cases; colony counts on settle plates were higher on the side opposite to the hand the nurse used to withdraw the catheter than on the same side, and the catheters tended to be withdrawn diagonally across the patient's face past uncovered and open eyes (106). Similarly, use of nasogastric tubes may be expected to cause eye infections, although this association has not been demonstrated.

Pediatric Intensive Care Unit

Endemic nosocomial infection rates in pediatric intensive care unit (ICU) patients have been reported as 11.0% in an 18-bed unit in a pediatric

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...tory tract infections ...3 and 17.2% of noso- ...hospitals (4, 5, 10, ...difficult to assess ...asymptomatic infec- ...(up to 2% of ...) and the need for ...on or bladder aspira- ...minated urine in infants ...healthy adolescent fe- ...fusion, a statistically sig- ...ween the number of ...the number of hours of ...and the subsequent de- ...infections has been ...intermittent catheteriza- ...ter and more effective ...than ileal loop ...).

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...nosocomial eye infections ...atients resulting in blind- ...was traced to bacterial ...suctioning (106). Only ...percent colony counts ...on the side opposite ...withdraw the cath- ...eter, and the catheters ...diagonally across the ...and open eyes (106). ...tubes may be ex- ...though this as- ...unproved.

...sive Care Unit

...infection rates in pediat- ...CU) patients have been ...unit in a pediatric hospital (4) and 3% in a 16-bed unit which admits some children (107). Sixty percent of all nosocomial bloodstream infections occur there (4). As in the adult patient, multiple factors—including a depressed immune system due to underlying illness, invasive devices, exposure to antibiotic-resistant bacteria, emergency procedures performed without proper aseptic techniques, and the close proximity of patients to each other—may account for the high incidence.

Epidemic disease has been described. In three outbreaks due to *P. aeruginosa* and *E. cloacae* no source was identified, although some environmental contamination was documented (89, 90). Two outbreaks appeared to originate with a patient transferred from another hospital (89). The highest attack rates have been in neonates (89, 90). Intrinsic contamination of tracheal irrigant with *Pseudomonas pickettii* was documented in one outbreak (108). Control measures have been directed at removal of the source and improved infection control practices. In the outbreak of a gentamicin-resistant organism, gentamicin was withdrawn before the outbreak was controlled (90). The importance of viral infections in the ICU is now being recognized (109). Two clusters of nosocomial herpes simplex infections with two separate genetic strains were described in a pediatric ICU (110). Three nurses developed herpetic whitlow and a fourth acquired gingivostomatitis. The index case in the first cluster was a child with encephalitis and oral herpes. A 2-year-old girl acquired severe gingivostomatitis from one of three infected nurses (110). Additional information about risk factors is required (111–113).

Burn Units

There are few data on infections in children in burn units, although the susceptibility to bacterial wound infection and sepsis is well recognized. The care of the burned child does not differ from adults except for a greater probability of group A streptococcal sepsis. Nosocomial herpes simplex and varicella infections have been described (114).

Immunosuppressed Patients

Immunosuppressed patients are at high risk of nosocomial infections because of (*a*) impaired host defenses, (*b*) the need to perform invasive diagnostic or therapeutic procedures, and (*c*) alterations in normal flora. *S. aureus* bacteremias were preceded by a primary site of infection in 58% of 45 episodes. Primary sites of infection included an infected finger secondary to finger puncture for blood sampling, infected hyperalimentation lines, an intravenous catheter, a pierced ear lobe, a biopsy site, and a paracentesis site (115). In another series of *S. aureus* sepsis, primary sites similarly preceded 57% of episodes and included finger punctures for blood sampling (5) and intravenous catheter sites (10, 116).

Others have noted the emergence of *S. epidermidis* as an organism responsible for 12.7% of all septicemic episodes in a 30-month period (117). Unlike other groups who have associated the increased incidence of this pathogen with the use of long term indwelling catheters (79), they report two fatal episodes of *S. epidermidis* septicemia occurring in patients who did not have indwelling intravascular catheters. The incidence of sepsis was similar in patients with both peripheral and central lines, and antecedent throat and rectal colonization did not precede sepsis. They postulate two groups of patients who are undergoing intensive chemotherapy and prolonged hospitalization who are at risk for *S. epidermidis* septicemia. The first group have had significant prolonged breaks in the integument often with indwelling catheters, while the others have neoplastic disease in relapse with absolute granulocyte counts of less than 100/mm^3/for 3 weeks or more.

Children with congenital immunodeficiency syndromes experience an increased severity of infection with parainfluenza virus (118, 119), respiratory syncytial virus (120), adenovirus (121), and rotavirus (122). Bacteria including *Clostridium difficile*, protozoa including *Cryptosporidium*, and other diarrheal agents may also be associated with overwhelming diarrhea, chronic infection, and death, particularly in bone marrow transplant recipients (123–125).

Alterations in Normal Flora

The three factors which seem to alter normal flora are (*a*) severity of illness, (*b*) duration of hospitalization, and (*c*) antibiotics (126). Antibiotic therapy was the main risk factor in determining the colonization rate of the external ear canal with potentially pathogenic flora in one study in which gram-negative bacilli or yeast were found in 58% of patients receiving antibiotic therapy, compared with 17% of patients hospitalized for 10 days or longer and only 3% of patients hospitalized for short periods (127). Thirty percent of children studied on admission to hospital had positive yeast isolates, with the

percentage increasing with each week of hospitalization. By the fourth week, 80% of those still in hospital were colonized (128). The relative importance of confounding factors, such as antibiotics, corticosteroid therapy, intravenous therapy, parenteral alimentation, surgery, intravenous or urinary catheters, was not assessed. Asymptomatic nasopharyngeal colonization with *H. influenzae* type b of 11% of staff performing respiratory therapy in a pediatric chronic disease hospital has been documented (129).

MODES OF TRANSMISSION OF INFECTION IN THE PEDIATRIC HOSPITAL

The routes for acquisition of new organisms are multiple (Fig. 28.1) and include contact (both direct from one patient to another and indirect via contaminated fomites or droplets produced through coughing and sneezing), vehicles (for example, leafy vegetables contaminated with gram-negative organisms, water, food, drugs, blood products), and airborne (either droplet nuclei or dust particles or small particle aerosols < 10 μ mass median diameter which are contaminated with bacteria fungi or virus). Hospital construction and building materials can disseminate fungal spores which cause disease in immunocompromised patients. Insect transmission does not appear to be a major problem in North American hospitals.

The problem of infections in children is aggravated by the normal behavior of the children themselves (130–134).

1. Toddlers between the ages of 2 and 4 years have been clocked at putting a hand or object in the mouth every 3 minutes.
2. Close contact of young children is almost constant unless children are specifically segregated.
3. Younger children are incontinent of feces before toilet training.
4. Younger children lack proper personal hygiene because of their age.

Of special concern in the pediatric facility are the role of visitors, contaminated fomites, and asymptomtic carriers of potential pathogens.

Visitors

The number of visitors may exceed the number of patients, and the parent-visitor may spend up to 24 hours a day and 7 days a week in the hospital. They may move freely in and out of waiting rooms, lobbies, cafeterias, washrooms, hallways, elevators, and may have contact with other children at home and in day care facilities, before returning to the patient's room. Parent-visitors often freely handle other children in a multibed room. The nurse, on the other hand, often spends less than 3 hours a day and the doctor less than 1 hour a day in the patient's room. Additional information is needed on the role of the parent-visitor in transmission (135, 136).

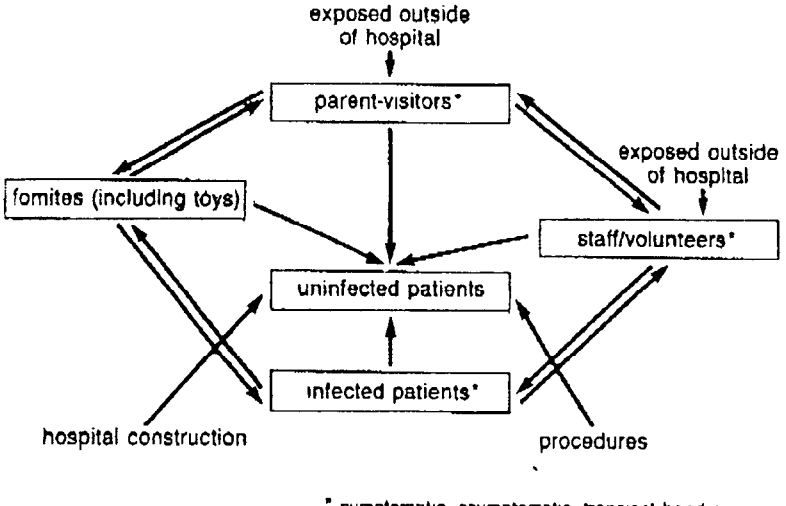

Figure 28.1. **Routes for acquisition of communicable diseases in the pediatric hospital. (Modified from Hall CB, Geiman JM, Douglas RG, Meagher MP: Control of nosocomial respiratory syncytial viral infections. *Pediatrics* 62:728–732, 1978.)**

Fomites

Removal of respiratory and enteric viruses from contaminated surfaces may be important in control of nosocomial infection and is covered in detail in Chapter 18 and under respiratory and gastrointestinal infection control later in this chapter. Tremendous numbers of virus are excreted in respiratory secretions (137–139) and stool (140–142), and persistence of virus on surfaces for hours and even days may be common (143–146). Rotavirus, as well as hepatitis B, may be resistant to killing by routinely used disinfectants (147–152). Increased environmental contamination has been described during epidemic diarrheal disease in day care settings (145, 153, 154). Toys may be particularly important vectors (153, 154).

Asymptomatic Carriers

In Providence, in 1912, Chapin noted "Studies in hospitals and elsewhere have confirmed the belief that air is of minor importance in the spread of disease . . . the carrier is very important, if not the most important factor in the spread of the disease . . ." (155). This may be equally true today as incubationary and convalescent carriage are documented in children, parent-visitors, and staff as well as asymptomatic infection with many viral and bacterial pathogens.

PRIMARY PREVENTION AND PRE-EXPOSURE MANAGEMENT

Transmission of infection may be interrupted through efforts directed at the patient and parent-visitor, environment, and hospital personnel. Hand washing is of particular importance.

The Patient and Parent-Visitor

In considering this aspect of nosocomial infection prevention, the three traditional approaches to the control of infectious diseases in the host must be examined: immunization, chemoprophylaxis, and general infection control practice.

Immunization of Infants and Children

The best means of reducing the incidence of the vaccine-preventable diseases of childhood (diphtheria, pertussis, tetanus, polio, measles, mumps, and rubella) is by having a highly immune population (156). Particular attention must be paid to the immunization of premature infants, long stay patients, patients with nonprogressive and chronic diseases, neurologic disorders, and immigrants from nonimmune populations (157, 158). Enforcement of day care and school immunization requirements should be undertaken, and a comprehensive and accurate immunization record should be established for each newborn infant, maintained by the parent (156), and included in the hospital records.

Chemoprophylaxis

While this is more appropriately considered under treatment, prompt initiation of appropriate therapy may be successful in decreasing the reservoir of infectious agent in hospital even in situations where such therapy would not necessarily be recommended in outpatients, e.g., trimethoprim-sulfamethoxazole in enteropathogenic *E. coli* diarrhea, so that the risk of transmission to others is minimized.

General Infection Control Practices for Outpatients

Wherever possible, patients with an infectious disease, transmitted by the airborne route should be escorted through a separate entrance, avoiding waiting areas, into a single room in a separate area of the clinic for prompt assessment. While airborne disease transmission has not been documented in hospital clinics, measles has been contracted in a physician's office (159, 160). Patients at high risk of life-threatening disease from respiratory infection (e.g., the young infant (161), patients with congenital heart disease (162), and immunosuppressed patients (120)) should be similarly sent directly to a single room rather than remain in a common waiting area. Such patients who make repeated visits to the hospital may be identified by a card. Patients in observation areas should be managed according to general isolation guidelines, and high risk patients should be excluded from these areas. The hazards of immunosuppressed patient clinics have not been elucidated (135). A report of recovery of *P. aeruginosa* in dried sputum for more than 1 week and from sinks, soap, baths, toys, tables, brushes, cloths, and air in a cystic fibrosis clinic as compared to isolation cubicles where patients were treated suggested that it may be appropriate to segregate colonized and noncolonized patients and arrange for visits on separate days in the outpatient clinics (163). Pulmonary function laboratories in which these patients are tested should follow good infection control technique (164).

General Infection Control Practices for All Inpatients

Contagion Check. A communicable disease survey or "contagion check" is required for every pediatric patient. This survey should be completed prior to admission so that elective patients with infections may be excluded and appropriate ward placement and isolation implemented as indicated. This is particularly important during peak virus activity in the community. Essential components include the immunization history for measles, mumps, rubella, polio, diphtheria, pertussis, and tetanus; a history of exposure to infectious; any symptoms of infection, including cold, cough, vomiting, diarrhea, skin rash, or fever; and recent previous hospitalization requiring isolation (9). Infection control personnel must be available to review histories and physical findings at the request of admitting staff. It may be prudent to isolate patients transferred from other hospitals if the risk of colonization with resistant organisms acquired in that hospital is likely. This applies in particular to patients transferred from other hospitals in parts of the world with a high prevalence of methicillin-resistant *S. aureus* (e.g., Eastern Europe). Infants at high risk for severe or complicated RSV infection should not be electively admitted to the pediatric wards during an RSV outbreak (20).

Playroom. Restriction of children from the playrooms for the 48 hours after admission may be appropriate while the presence of infectious diseases previously overlooked or still in the incubationary phase on admission is ruled out. The use of nonporous toys which can withstand rigorous mechanical cleaning with running water for at least 10 second, high level disinfection, or alternatively sterlization after use by infected patients and those with high rates of hand-mouth contact is desirable. Stuffed toys should be suspended out of reach or provided for personal use by selected patients. Floors should be kept clean since younger patients may use the floor as a playground (165).

General Infection Control Practices for Infected Inpatients

Isolation Precautions. Authoritative sources for isolation procedures are available (157, 166–169). With additional studies, it will be necessary to revise some recommendations (166). The importance of prompt isolation of all infected patients and those with presumed or possible infections, including those with colds or chronic diarrhea, until an infectious etiology has definitely been ruled out cannot be overemphasized. Isolation requirements should be routinely recorded in the admitting orders. The new CDC guidelines (166) have eliminated "reverse/protective isolation" for immunocompromised patients for reasons discussed in Chapter 29. Contact or "mini-strict" isolation—that is, masks for contact within 3 feet, gowns and gloves for physical contact—has been introduced as an alternative for uncertain isolation situations where small particle aerosol transmission is not likely (166, 167). Contact isolation is recommended for infants and young children with viral respiratory symptoms. Respiratory isolation is recommended for infants and children but not for adults with *H. influenzae* pneumonia. Cohorting as described in Table 28.7 may be appropriate if all patients are infected with the

Table 28.7. General Guidelines for Use of Cohort Isolation*

1. Patients should be separated into cohorts of infected ("dirty") and noninfected ("clean") patients.
2. Only persons with proven or suspected infection should be admitted to the infected cohort.
3. All exposed (potentially infected) individuals should be included with the cohort of infected patients. In some instances, the potentially infected cohort may be separated into a third cohort.
4. The infected cohort should be closed to new, uninfected admissions, and all new, uninfected admissions should be placed with the uninfected cohort.
5. Personnel working with the infected cohort should be immune to the illness in question by either previous history of illness or vaccination whenever possible.
6. Personnel should be assigned so that separate groups work with the infected and uninfected cohorts whenever possible. Crossover between cohorts should be discouraged to minimize the risk of cross-infection of the uninfected cohort.
7. When personnel must work in both areas, they should work in the "clean" area first, then work in the "dirty" area.
8. The infected cohort area will be closed as patients are discharged from the hospital and may be used for new, uninfected admissions after thorough cleaning of the area and its equipment.

*From Valenti WM, Menegus MA: Nosocomial viral infections. IV. Guidelines for cohort isolation, the communicable disease survey, collection and transport of specimens for virus isolation and consideration for the future. *Infect Control* 2:236–245, 1981.

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same pathogen. Cohorting by clinical syndrome rather than by etiologic agent is generally unacceptable, but is often all that is possible in patients infected with viruses or enteric bacterial pathogens because of delays in specific diagnosis.

Gowns should be worn if patient contact is likely to lead to direct soiling of garments (166, 167) or if the organism is particularly contagious or virulent, e.g., methicillin-resistent *S. aureus*. Masks have not been shown to be of value in the prevention of nosocomial spread of RSV infection in either patients (170) or staff (171). Because coughs and sneezes result in the production of large particles which fall to the floor within about 3 feet of their origin, any exposure at this distance may be minimized by masks (167). In the case of smaller particles in which aerosol transmission can occur from highly contagious illnesses such as varicella, masks are thought to be of use (167). Gloves have been recommended when personnel have contact with the infected area of babies with diarrhea for aesthetic reasons (166) and as a reminder to wash hands (167).

Effects of Isolation. Little is known of the psychologic effects of isolation on the hospitalized child. Children in isolation may feel that they are being punished and rejected and may therefore be at risk of withdrawal and regression (172). Swedish workers have reported no negative effects of isolation provided that the child can observe the staff (165). Children raised in reverse isolation may experience difficulty with attachment behavior, although difficulties with emotional development may be modified (173, 174).

Diagnostic Investigations of Isolated Patients. These should be deferred if possible or scheduled at the end of the day in hospital areas where management of such cases has been clearly delineated (175).

Discharge. The charts of patients colonized with multiply resistant organisms which may persist for months should be identified on discharge so that the patients are isolated on subsequent admissions. Alternatively, parent letters or Medical-Alert bracelets may be provided. Ideally, convalescing infected patients should be discharged and readmitted for elective investigation to minimize problems associated with convalescent carriage of infective agents.

Visitors

It is advisable that visitors under 12 years of age be permitted only under special circumstances and after special arrangements have been made with the charge nurse or responsible physician. A "contagion check" as for an inpatient must be completed and the need for strict parental supervision of these sibling-visitors stressed. Parents should be instructed on hand washing before and after contact with their own child and the necessity of handling only their own child. Nosocomial pertussis (176), herpes (177), and RSV (20, 178) infections have been traced to parent-visitors, and their role in introduction of other respiratory and enteric pathogens is strongly suspected.

The Environment

Design of Facilities. The ideal design is not known. The pattern of transmission of RSV on the wards during outbreaks suggests that large open wards allow greater transmission than wards composed of smaller rooms (Table 28.8) (20, 179–182). Placement of each patient in a single room will almost certainly minimize the risk of nosocomial infection through facilitation of hand washing and disinfection but will not eliminate the risk (181, 183). It has been said that the sick child should be able to see adults (165). Some guidelines are available, and it appears that at least in the nursery population, increasing bed space per patient may result in a lower rate of infection (184), although others have not found this to be essential in adult populations (185). The importance of disinfection of the environment and toys has been discussed under "Methods of Transmission."

Hospital Personnel

The subject of employee health (169, 186–189) including the pregnant employee (190) is discussed in Chapters 12 and 13. The patterns of illness occurring in adult contacts are noted in Table 28.9. All staff should have completed a primary series of tetanus and diphtheria immunizations with boosters every 10 years, and all born after 1956 should have proof of immunity to measles. Rubella vaccination and annual tuberculosis skin testing should be conditions of employment. Mumps and polio protection is also advisable; pertussis immunization is not routinely required. Annual influenza immunization is recommended. The need for hepatitis B immunization of staff in pediatric facilities is unclear. One pediatric center has documented no increase in risk in a supposedly high risk population over a control population using hepatitis B surface antibody as a marker (191).

The need for careful education and screening

Table 28.8. Nosocomial Respiratory Virus Infection on Pediatric Wards with Differing Design and Infection Control Procedures Reported in the Literature

Reference	Agent	Time Course (Months)	No (%) of Patient Contacts with Nosocomial Respiratory Infection
183	RSV	2	13
	Rhinovirus		2
	Parainfluenza virus Type 1		1
246	Parainfluenza 3	15	36 (18)
179	RSV	4	15
	Influenza A		16
	Parainfluenza		19
251	Influenza A	1	12 (70)
181	Rhinovirus	4	4
	RSV		3
	Parainfluenza type 3		2
	Influenza A and B		2
	Symptomatic		4
			15 (17)
182	RSV	2	8 (19)
180	RSV	24	25
	Influenza		18
	Parainfluenza		12
	Adenovius		10
	Rhinovirus		9
	Symptomatic		95
			169 (1.6)
178	RSV	2	19 (37)
236	Influenza type C	12	17 (85)
22	Adenovirus type 7b	1	5 (1.0)

of all employees and students during a prework health evaluation, assessment at the time of acute illnesses, and meticulous follow-up of all exposures 24 hours of the day, 7 days of the week cannot be overemphasized in the pediatric hospital (188). An information sheet dealing with diseases and exposures such as that in Table 28.10 may be reviewed with all employees and students before employment to advise them of what they may acquire from and transmit to patients. This necessarily includes medical and surgical attending and research staff, house officers, nurses, support staff, ancillary personnel, and their students.

Disease in pediatric hospitals due to rubella, herpes simplex, (110), influenza A, respiratory syncytial viruses (170, 192), pertussis (193, 194), varicella (35, 36, 195), scabies (196), mumps (197), respiratory and diarrheal pathogens has been traced to and from personnel. Infants on a pediatric ward have been exposed to a nurse with diphtheria but no disease occurred in contact infants (198).

Precautions for Special Patients

Pediatric Intensive Care Unit Patients

The pediatric ICU should be given high priority in an infection control program. Adherence to basic practices, such as hand washing and good device management, should be stressed and monitored through a surveillance program and appropriate epidemiologic studies as in the adult ICU.

Immunosuppressed Patients

Infections in immunosuppressed pediatric patients resemble those in adults (199). Efforts to minimize pathogenic endogenous flora include prophylactic antibiotics and antifungals, colonization and suppression therapy, isolation and surveillance cultures, as well as cytomegalovirus prophylaxis with immunoglobulins as described in Chapter 29 (200–205).

Immunization must be kept up to date because of the increased risk of exposure in hospitals and clinics and the increased severity of measles (206, 207) and polio (208). It is common practice to

Table 28.9. Patterns of Occurrence of Diseases in a Pediatric Hospital*

Pattern of Occurrence	Example
Manifestations of infection primarily in children	Herpes simplex
Infection affects children and hospital staff	Respiratory syncytial virus
Infection is inapparent in children, but is likely to be apparent in hospital staff	Hepatitis A virus
Infection is inapparent or mild in children and in adult contacts, but may have serious consequences for the fetus of a pregnant contact	Cytomegalovirus, rubella

* Modified from Goodman RA, Osterholm MT, Granoff DM, Pickering LK: Infectious diseases and child day care. *Pediatrics* 74:134–139, 1984.

Table 28.10. Occupational Health Infectious Diseases Information Sheet

If you have *diarrhea*—wash hands very carefully after using the bathroom and before touching patients or their equipment. Try to avoid working with children less than 2 years old and with those with metabolic defects.

If you have a *cold*—wash hands very carefully before touching patients or their equipment. Wear masks and gowns for any direct contact with patients less than 2 years of age. Minimize contact with infants, immunodeficient or congenital heart patients.

If you have a *cold sore*, cover it with a mask or Band-Aid and wash hands thoroughly before touching any patient. Avoid contct with burns, immunodeficient patient, patients with skin disease, and newborn infants.

If you have a constant *pain* in one area, watch carefully to be sure that shingles are not developing.

If you are exposed to chickenpox at work or home and have never had chickenpox, lived in the same house with or cared for someone with chickenpox, please check with occupational health or infectious diseases to determine if and when you should go on a leave of absence.

If you are exposed to measles and have never had measles or immunization against measles, please notify occupational health or infectious diseases before working.

If you are exposed to blood through contact with mucosa, eye, skin, please contact occupational health or infectious diseases to assess the need for hepatitis B prophylaxis.

If you are exposed to whooping cough and develop a cough, inform your doctor that you have had this contact so that he may take further tests and notify occupational health or infectious diseases before working.

If you have or are exposed to any other infections, please check with occupational health (daytime) or infectious diseases (nights and weekends) before working.

defer administration of all live virus vaccines until no less than 3 months after all immunosuppressed therapy has been discountinued (157), while administration of killed vaccines may continue since the majority will respond (209). Revaccination with DT-polio of previously adequately immunized children is recommended soon after cessation of therapy (210). Exposure of susceptibles to children excreting vaccine strains of poliovirus should be avoided. Although children receiving immunosuppressive therapy from leukemia make antibody less effectively than normal children, the majority will develop sufficient antibodies after immunization to modify natural infection favorably. Response to influenza vaccine appears adequate (211–213), although diminished responses may be noted in patients receiving long term chemotherapy for neoplastic diseases (212, 213).

Avoidance of urinary catheters, indwelling venous catheters, and frequent changes of steel needles is advisable (79). Meticulous skin preparation must antecede any break in the skin (115–117). Unusual presentations of highly communicable disease may pose problems. Measles pneumonia, for example, may be unaccompanied by rash (207). Sequelae from respiratory (118–121, 214–216) and enteric (122–125, 217, 218) pathogens may be life-threatening or fatal. Patients likely to receive multiple blood transfusions should receive hepatitis B vaccine (157) because screening of donors for hepatitis B surface antigen is not 100% effective. There appears to be an increased incidence of chronic persistent and chronic active hepatitis in leukemic children (219, 220). Patients exposed to varicella or presenting with a rash should be instructed to seek immediate immunoglobulin prophylaxis and avoid the hematology/oncology clinics. Regular screening for varicella antibody using a sensitive and specific test, such as the fluorescent antibody membrane antigen test, is advisable in order to reduce unnecessary use of varicella-zoster immune globulin, although immunosuppressed history-negative, seropositive patients can occasionally develop mild disease (221). Patients should be moved from wards adjacent to or undergoing demolition or construction to minimize the risk of aspergillosis (222–224). Immunosuppressed patients exposed to active tuberculosis should receive rifampin and a second drug, e.g., ethambutol, for 6 months (157). Because *H. influenzae* infections have been described in an older age group (4 to 12 years) of immunosuppressed patients and infections may present without a focus, household and close contacts of those

with *H. influenzae* disease should receive prophylaxis if there is an immunosuppressed child of any age in the household (225).

The National Institutes of Health in Bethesda have carried out a major and innovative campaign directed at patients to emphasize hand washing and to teach patients to protect themselves, so it is not uncommon for a child to inform a forgetful physician that his hands should be washed before examination (167).

Precautions for Specific Diseases

Prompt recognition of children with infectious diseases in need of isolation is essential.

Viral Respiratory Diseases

General guidelines may be found in Table 28.11. Influenza vaccine is recommended for high risk groups, including patients with congenital heart disease, cystic fibrosis, severe asthma and other chronic lung diseases (158, 226–232) as well as the immunosuppressed patient.

Diarrheal Diseases

General guidelines may be found in Table 28.12. Patients with acute vomiting or chronic diarrhea should be viewed as potentially infected and should be isolated until infection, particularly with *Salmonella* sp. and *E. coli*, has been ruled

Table 28.11. Summary of Options for Control and Prevention of Nosocomial Respiratory Virus Infections

1. Prompt contact isolation of all patients ≤ 2 years old with any respiratory symptom including the common cold or cohorting of infected infants preferably by etiologic agent where individual isolation is not possible.
2. Hand washing.
3. Use of gowns if soiling is likely.
4. Cohorting to staff to infants infected by the same etiologic agent.
5. Isolation of high risk contact infants, i.e., infants with congenital heart disease, immunosuppressed patients, and premature infants with pulmonary problems, at distances greater than 6 feet from infected infants. Assign asymptomatic staff, preferably with long term pediatric experience, to their care.
6. Limitation of visitors.
7. Shorter hospital stay.
8. Avoidance of elective admissions and elective surgery.
9. During influenza A outbreaks, chemoprophylaxis with amantadine for unimmunized personnel and high risk patients. The use of influenza vaccine has been discussed under "Primary Prevention and Pre-exposure Management."

Table 28.12. Control and Management of Nosocomial Gastroenteritis

1. Define the causative epidemic strain through studies for bacteria, viruses, and parasites. Strains should be typed if possible and antibiotic sensitivity patterns determined if appropriate. Failure to detect a pathogen is not a reason to stop enteric precautions in a child with acute diarrhea because unidentified, presumably contagious agents are common. Serologic tests are of no practical value.
2. Obtain a stool specimen (in consultation with laboratory staff) from all infants because asymptomatic carriage of organisms may perpetuate the outbreak. Ideally the stools of all staff (or at least ill staff) are also examined.
3. Remind staff of hand contamination with enteric pathogens following defecation.
4. Isolate the index case in a single room and isolate the roommate in the original room. This contact room should be closed to admissions for the duration of the incubation period (157). Since some of these patients will already be incubating the contagious diarrheal agent, they should not be transferred into a room with unexposed children.
5. Close the ward to all new admissions and reduce the ward census as rapidly as possible depending on the agent involved and the number of symptomatic children. Close the playroom. Counsel the family carefully on symptoms of disease, fluid management, and antibiotic therapy (if required) prior to discharge. Parents and other household contacts of infants should be instructed in the use of enteric precautions appropriate to the home. Disposal of stools and diapers and the need for careful hand washing after contact with the infant must be emphasized.

out. During community outbreaks, it may be appropriate to reduce enviromental contamination through weekly cleaning of infant and toddler rooms with concurrent bathing of each child and placement into a clean crib. Immunosuppressed patients, particularly those having undergone bone marrow transplant who are at risk of fatal disease in association with infection with enteric pathogens, infants and children in the first year of life who are at a higher risk of overwhelming sepsis and death with bacterial pathogens (233), and patients unable to adjust to fluid loss such as some metabolic patients, should not share personnel or be placed in rooms with staff caring for infected patients (233).

Multiply Resistant Organisms

The risk of transmission may be minimized by isolation of patients coming from other hospitals or other countries where multiply resistant organisms are endemic until nasal, rectal, and wound swabs are reported as negative. Patients once colonized may remain so for months and should be identified as such in the hospital chart for future admissions.

Aspergillus

Some cases of aspergillosis may be prevented by adherence to precautions taken at the time of construction as discussed under "Cutaneous and Other Fungal Infections Originating in Hospital" (222, 223, 234).

Hepatitis A

Prevention depends on the routine use of basic infection control practices including prompt isolation of patients with diarrhea regardless of whether or not an infectious process is suspected (235, 236).

Hepatitis B

Recommendations for the use of vaccine in pediatric patients are under review. Unvaccinated children born to infected patients and the institutionalized retarded probably provide the greatest risk (157).

Skin Infections

Patients with eczema who have secondary infections shed massive numbers of organisms, usually *S. aureus* and group A streptococcus. Care must be taken to avoid transmission from and to (e.g., herpes simplex) these patients.

Pediculosis

Although pediculosis is a widespread problem among school-age children, lice are unlikely to be transmitted to other patients except in ambulatory chronic care patients such as are on a psychiatric ward where visual screening of all residents at the time of admission is appropriate.

Scabies

Prevention of outbreaks requires screening of patients for skin problems and appropriate diagnostic tests. Color pictures in the ward procedure book may be of assistance.

SECONDARY PREVENTION CONTROL AND POSTEXPOSURE MANAGEMENT

This review of pediatric nosocomial infections by clinical syndrome includes the prevalence of agents in hospitalized children, nature and frequency of nosocomial outbreaks, information about mode of transmission, susceptibility and reinfection, and an approach to control and management.

Viral Respiratory Infections

Prevalence. A tremendous multiplicity of agents has been associated with viral respiratory illnesses in children. They generally vary in ability to cause specific syndromes, depending on the agent and the age of the patient. For example, the most common cause of wheezing associated with respiratory infection in children under 3 years of age is RSV, whereas *Mycoplasma pneumoniae* may be the most frequent isolate for school age children with wheezing illness (237). In a study of patients less than 5 years of age hospitalized with acute lower respiratory tract infection in which an exhaustive search for infectious agents was made, a viral pathogen, most commonly RSV, was identified in 63% of cases (238). Infection with multiple agents occurred in 5% of cases. Rhinovirus was associated with disease indistinguishable from RSV, parainfluenza, and adenovirus. *M. pneumoniae* is probably also important but was not diagnosed. In a study of patients with croup, 74.2% of all isolates were parainfluenza viruses, although RSV, influenza, and *M. pneumoniae* may also cause this clinical syndrome (239). Other countries including Sweden have similarly reported a high incidence of RSV (240), and indeed acute respiratory infections in children are a major global public health

problem (241). In other parts of the world such as New Guinea, bacterial pneumonia may be more common than pneumonias caused by viruses (242).

Community epidemics of RSV occur regularly from midwinter to early spring, and during this period many children admitted to the hospital with respiratory symptoms are infected with RSV (243). During peak epidemic influenza virus activity, influenza virus may interfere with the spread of other major respiratory viruses (244). Repeated infections, often of severity equal to the primary infection in children, are the rule before 3 years of age on exposure to RSV (24), and indeed repeated infections with parainfluenza (25) and influenza (230) may occur throughout life.

Outbreaks. A review of nosocomial outbreaks can be found in Table 28.8. The spread within the hospital of RSV, parainfluenza, and influenza A viruses during the period of their respective community epidemics is probably the rule rather than the exception. In contrast, nosocomial adenoviral epidemics may occur during a time of minimal community activity (22). Cross-infection is commonly traced to infected infants on the same or adjacent wards. In one report of 11 nosocomial infections, only 2 were acquired from infected roommates, the remainder presumably being introduced by staff and visitors (181). Most infected staff are symptomatic (20, 245).

Mode of Transmission. There are two major routes of transmission of respiratory viruses. The first is by *small particle aerosols* (< 10 μm mass median diameter). Aerosols produced by coughing, sneezing, or talking can transmit infection from one person to another over a considerable distance. Influenza, varicella, and measles viruses exhibit patterns of spread compatible with this mechanism. Other viral agents, such as RSV and rhinovirus, can be transmitted by mechanisms requiring *close person-to-person contact*, usually defined as a distance less than 3 feet separating the two persons. Large droplets produced by coughing or sneezing may spread the infectious virus directly to the skin or mucous membranes of a susceptible host or may contaminate the donor's hands and spread via *hand-to-hand contact or indirectly, via contaminated fomites.* In either of the latter cases, infection of the susceptible host is the result of autoinoculation from transfer of virus from the hands to the mucous membranes of the eye, nose, or mouth. Contagiousness, therefore, depends on the quantity of virus in nasal secretions, the effectiveness with which infected secretions are propelled into the environment through coughing, sneezing, or carried on hands, and how long the infectious virus can survive in the environment.

Parainfluenza type 3, RSV, and influenza A virus may be recovered from the nasopharynx for up to 6 days before the onset of symptoms, although they are most common in the antecedent 24 to 48 hours (137). The duration and degree of shedding of RSV are related to the age of the host and severity of illness (138, 139), with young infants and those with lung consolidation shedding virus for longer periods of time (139). Viral excretion persists in high titers until considerable clinical improvement has occurred. Parainfluenza type 3 virus may be recovered for prolonged periods of time, from 12 (246) to 30 or 40 days (137). Shedding for 1 week following onset of influenza A and RSV disease caused by influenza A and RSV is common, while 37% of cultures for influenza B are still positive during week 2 (137).

RSV (143) and influenza A and B (144) viruses may persist on environmental surfaces, as shown in Table 28.13, providing an opportunity for

Table 28.13. Fomite Contamination by Virus

Agent	Source	Countertops (Hard, Nonporous)	Rubber Gloves	Paper Tissue	Cloth	Skin
RSV (143)	Freshly obtained infant secretions and	8 hr	1 1/2 hr	30–45 min	1–2 hr	20 min
	by hands touching these contaminated surfaces for up to 25 min					
Influenza A Influenza B (144)	Throat swab isolates passed once in tissue cultures and	24–48 hr 24–48 hr		8–12 hr 8–12 hr	8–12 hr 8–12 hr	5 min 5 min
	by hands touching these contaminated surfaces for up to 5 min					

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hand contamination and subsequent autoinoculation. Inoculation of RSV into the eye or nose (247) and of parainfluenza into the nose or throat (the eye has not been studies) (25) results in infection in the susceptible. Hand-eye or hand-nose contact is a normal part of human behavior, occurring once every 2 to 3 person hours of observation, during Grand Rounds, and several times during a 20-minute infant feed (248, 249). Influenza infection is most efficiently induced in volunteers by fine particle aerosols, although the role in natural transmission is not known (250).

Respiratory Syncytial Virus

Outbreaks (170, 179–183, 192). Children who are infected on admission are sources of RSV and may cause symptomatic infections in 40 to 60% of contact infants and 50% of hospital staff (20). Case-control studies have shown that risk of infection with RSV is affected by duration of hospitalization and by ward design. Open wards have the highest rates of cross-infection (20, 179–182).

Mode of Transmission. Risk correlates with the closeness of person-to-person contact. Only those staff members who cuddle infected infants or touch possibly contaminated environmental surfaces immediately surrounding the infant become infected, suggesting that airborne spread is not important (20, 251).

Control and Management (Table 28.11) Complete control will be difficult until antiviral agents or vaccine is available to patients and staff. While ribavirin looks promising, delivery is cumbersome and often impractical. Teratogenicity will preclude widespread use in female hospital staff of childbearing age (252–254). Long term pediatric experience and exposure to patients for less than 30 hours/week have been associated with lower rates of infection in hospital staff (171). The use of gowns and masks when studied prospectively did not decrease the acquisition of symptomatic respiratory infections in patients (170) or medical personnel (171) caring for infants. Masks continue to be recommended for close contact of 3 feet or less by some authorities (166).

Parainfluenza Type 3

Outbreaks (179–181, 183, 246). Twenty percent of 197 hospitalized infants and children less than 18 months old who were in contact with parainfluenza 3 virus acquired infection, usually during a cluster of index community-acquired cases and between the fourth and fifteenth day of hospitalization. Acquisition generally occurred after infants and children were removed from coupettes into low humidity environments (246).

Control and Management See Table 28.11.

Influenza

Outbreaks (179–181, 255, 256). High fever was the major presenting finding occurring in a ward outbreak involving 12 or 29 (71%) children hospitalized more than 1 week. Although the presence of clinical illness can be used to identify patients infected with influenza, the proportion of asymptomatic influenza infection may be high (257). Influenza C was removed from one employee, and two others had serologic evidence of acute influenza C virus infection during an outbreak of influenza-like illness in employees in the pediatric clinic at the University of California, Los Angeles Hospital. Forty-six percent of children under 5 years of age lack antibody. In a survey of children's residence, fever, nasal discharge, and sneezing developed in 85% of 20 children and 22% of 9 staff with confirmation of influenza C infection in 65% of children and 13% of staff (256).

Control and Management (Table 28.11). The prophylactic efficacy of daily amantadine in reducing the incidence of influenza virus infection in children has been demonstrated (258–260). It prevented disease in 50% of recipients in a hospital for the mentally retarded (260). Staff and patients at risk for severe disease should be immunized (157, 158, 226–232).

Adenovirus

Outbreaks. In a 1-month outbreak of adenovirus type 7b disease in a children's hospital in San Diego, four patients who acquired the disease died (22). Extensive cross-coverage of nurses from different units, the use of nurses per diem and cross-coverage by respiratory therapists, house officers, phlebotomy teams, and dietary workers may also have been responsible for spread. Over a period of 2 months, 18 adenovirus type 3 infections occurred in patients aged 4 to 12 years on a ward to which an infected 7-year-old girl was admitted (261). Symptoms of fever and conjunctivitis were present. High titer adenovirus immune serum globulin, if available, may be of use in controlling the disease (262). Restriction enzyme analysis may provide a more rapid means of discriminating between patient isolates during a nosocomial outbreak (263, 264).

Control and Management (Table 28.11).

hospitalization of institutionalized infants during adenovirus outbreaks may be considered (264).

Morbidity Mortality and Cost

Prolongation of hospital stay by 5.8 to 11 days for children with pneumonia and upper respiratory infections has been reported (161). Over a 6-year period, 37% of infants hospitalized with congenital heart disease and RSV infection died. Most infections were nosocomially acquired. Pulmonary hypertension was present in 72% of cases (162). Similarly infected children immunosuppressed through malignancy or primary disease were at risk of more severe disease (120). In children in a transplant unit at the time of a parainfluenza 3 outbreak, the frequency of rejection was generally increased, although outcome in terms of patient survival at 6 months was not affected (265). Occasional deaths may occur and hospitalization may be prolonged. The morbidity of influenza in children in general (257, 267, 268) and particulary in children with cancer (269) or chronic asthma (229) and the occurrence of repeated infections (230) with exposure to agents reaffirm the importance of reducing nosocomial disease. As well as lower respiratory disease, influenza may cause a nonspecific febrile illness and a variety of neurologic syndromes, including encephalitis, encephalopathy, meningitis, and Reye's syndrome. Types of underlying disease putting children at greatest risk, such as preexisting heart disease, immunosuppressive disorders, chronic pulmonary disease, diabetes mellitus, chronic renal disease, neuromuscular disorders, and neoplasms (231), are generally extrapolated from adults. Adenovirus type 7 has a propensity to cause fatal disease in the immunocompromised host (22).

General Recommendations for Control and Management of Viral Respiratory Infections

Control measures are listed in Table 28.11. Hand washing with 3 to 10 seconds of rapidly running water before and after all patient contacts remains the single most effective method of reducing the incidence of nosocomial infection. Rapid viral diagnosis will allow identification of infectious patients to facilitate segregated patients at high risk of severe disease. A number of techniques are under investigation, including detection of viral antigens in respiratory secretions by fluorescent antibody (FA) and enzyme-linked immunosorbent assay (ELISA) and early detection of viral antigens in tissue culture (270, 271).

Diarrheal Diseases

Prevalence. Through population-based prospective studies in North America, annual rates of diarrhea during the first year of life have been estimated at 0.82 to 1.05/child (272–274). Rates in other parts of the world may be 5 times as high. In the day care situation the rate appears to be somewhat higher at 1 24 cases/year in the first 2 years with high attack rates in staff and family members (275). Serocpidemiologic data in developed and developing countries suggest that most children acquire antibody to rotavirus before 3 years of age (276–278). Among children admitted to hospital with gastroenteritis, viruses are recovered from 25 to 55% of patients, generally in the winter months and especially in those patients between 7 and 24 months of age (111, 279–286). Rotavirus diarrhea increases slightly in cool dry months (151, 287). Bacterial causes are identified in 5% or less of hospitalized patients with some exceptions (288). Agents such as *Salmonella edinburg* or *Vibrio cholerae* may circulate in hospital when there is little or no community activity (289, 290).

Complete epidemiologic data linking agents detected only by electron microscopy to disease are lacking, although fairly convincing evidence is available to show that noncultivatable adenovirus and calicivirus are indeed pathogens (287). A poor association of rotavirus with entities other than the classic fever-vomiting-diarrhea syndrome (284–286) indicates the need for serologic studies in determining the etiology of diarrhea (272). While susceptibility of infants and children to bacterial pathogens is virtually universal, susceptibility of staff to bacterial pathogens is variable. Repeated infections with the same or other subgroups of rotavirus are known to occur in all age groups, although repeated infections may be milder (291–295).

Outbreaks. Tables 28.14 and 28.15 summarize the outbreaks reported on pediatric wards. Diagnostic methods, incubation periods, assiduousness of case finding, and definition of the population at risk vary considerably. Rotavirus and adenovirus infections are probably grossly underestimated because of the lack of readily available diagnostic methods. Of 1173 patients with nosocomial gastroenteritis listed in Tables 28.12 and 28.13, viruses were implicated as the cause in 400 patients, *Salmonella* sp. in 489 patients, and other bacterial agents in the remainder. Multiple putative pathogens may circulate independently (296, 297, 299, 300, 303). An outbreak with a heterologous rotavirus population

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Table 28.14. Nosocomial Viral and Mixed Diarrhea on Pediatric Wards Reported in the Literature

Reference	Agent (No.)	No. (%) of Patients with Nosocomial Infection*	Time Course
296	Rotavirus (6) Adenovirus (6)	6 (23) 6 (32)	39 days 3 days
297	Rotavirus (75) Minireovirus (58) Adenovirus (31) Picorna/parvovirus (38) Astrovirus (11)	213	1 year
298	Reovirus-like agent (10)	12 (20)	24 days
299	Astrovirus (14) Astrovirus + rotavirus (5) Rotavirus (3)	22 (5)	4 months
300	Rotavirus (1) Minirotavirus (10) Calicivirus (7) Picorna-paravirus (1)	26 (16)	53 days
301	Calicivirus (7)	26 (77)	31 days
302	Calicivirus (4)	5 (83)	2 months
303	Rota (14) *Salmonella* (8) *Shigella* (1) *E. coli* (30) Parasites (3) *E. histolytica* (1)	77	1 year
304	Adenovirus (5)	5	3 months
305	Rotavirus (22)	37	11 months
306	Rotavirus (8)	8	3 months
284	Rotavirus (6)	6 (.03)	11 months

* Includes patients with one or more of the following: clinical disease, pathogen in stool, or serologic evidence of infection.

Table 28.15. Nosocomial Bacterial Diarrhea on Pediatric Wards Reported in the Literature

Reference	Agent	No. (%) of Patients with Nosocomial Infection	Time Course (Months)
289	*Salmonella edinburg*	299	32
307	*Salmonella indiana* (MDR)*	46	13
308	*Salmonella heidelburg*	55	4
309	*Salmonella wandsworth*	7	4
310	*Salmonella muenchen*	28 (7)	1
311	*Salmonella havana* (MDR)	44	6
312	*Salmonella typhimurium* (MDR)	26 (44)	3
290	*Vibrio cholerae* (MDR)	216	7
313	*Shigella sonnei*	13	1

* MDR, multiple drug-resistant.

with mixed patterns has been described (314). In only 10 of 25 cases of nosocomial gastroenteritis was concordance with a presumed index case roommate demonstrated (300). With the availability of tissue culture methods to recover rotavirus, asymptomatic shedding of rotavirus has been found in 15 to 60% of infants 7 to 24 months of age, much higher than in outbreaks using only

less sensitive electron microscopic or counterimmunoelectrophoresis techniques (272). The prevalences of asymptomatic rotavirus carriage in outbreaks has been lower than this (Table 28.16). Asymptomatic and symptomatic staff have been identified during outbreaks, and incidental pathogens such as *Camphylobacter* sp. or *Salmonella* sp. have been uncovered during screening. Their role in transmission is unknown, although asymptomatic carriers may be important in the maintenance of neonatal rotaviral outbreaks (315).

The following issues have been identified as factors contributing to outbreaks: multibed rooms; overcrowding; roommate with diarrhea; temporal relationship to infected patient (either same ward or moving to the room following discharge of an infected patient); sharing a cot; eating with fingers from a communal plate; transport of diapers outside the patient's room for diagnostic tests; handling of infants by parents of other children; common playroom, scale, bathing, and feeding facilities; multiuse lubricants; failure to transfer long stay patients to an isolation ward; contamination of sodium hypochlorite; and inadequate kitchen procedures. Nosocomial gastroenteritis appears to be most prevalent in children under 2 years, although age-specific attack rates for nosocomial disease are not available.

Mode of Transmission. Because rotaviruses and fastidious adenoviruses have not been cultivatable in tissue culture until recently, there have been no systematic studies of the mechanism of transmission of these aspects which cause most cases of infantile diarrhea. Rotavirus and other agents causing diarrhea are excreted in very large numbers in the feces of patients, with 100×10^9 viral particles/g of stool being visible by electron microscopy and as many as 2000 infectious virions/ml detectable by tissue culture (140,141).

Table 28.16. **Asymptomatic Carriage of Enteric Pathogens in Children during Nosocomial Outbreaks**

Reference	Agent	No. Recovered/ No. of Children Examined
296, 298, 300, 303	Rotavirus	2/82
296, 304	Adenovirus	1/85
300	Minirotavirus	8/25
300, 301	Calicivirus	5/38
299	Astrovirus	0/10

Extrapolating from data on rotavirus antigen there may be 1 mg of virus/ml of infected stool (142). Even larger amounts of infectious organisms are shed in bacterial diarrheas. The infecting dose in children is unknown (316, 317).

Rotavirus has been recovered from a variety of hospital surfaces, and in studies of suspension of fecal matter survival for up to 10 days on nonporous surfaces has been demonstrated (140, 145, 151, 154). Solutions containing organic iodine, hypochlorite, or quaternary ammonium salts as the principal active ingredient(s) are ineffective in inactivating rotavirus. Phenol-based products give variable results. Products containing 60% ethanol or inorganic acid(s) are able to inactivate the virus (147, 148, 150). Products appearing effective in the suspension have not always been effective in the disinfection of rotavirus-contaminated surfaces (149).

Hand carriage of enteric pathogens is probably very important (318). The hands of all attendants working with 147 children under 5 years of age admitted to the International Center for Diarrheal Disease Research, Bangladesh, were washed thoroughly in a sterilized bowl with 100 ml of tap water within 4 hours of admission of the first four children each day (319). A total of 78.6% of the attendants of 70 patients with rotavirus diarrhea and 19.5% of the attendants of 77 patients without were positive for rotavirus antigen. The hand washings of attendants of younger children with rotavirus diarrhea contained more rotavirus antigen than the hand washings of attendants of older children. Hand contamination following defecation in convalescent carriers of *Salmonella* sp. has been described (320).

Environmental contamination has been demonstrated in elegant studies involving piglets in a nursery (321–323). Contamination of the facility with porcine rotavirus increased with continuous use, causing a progressive increase in the incidence of infection and death. One-day-old piglets were introduced to a nursery every 10 days for a 2-week period so that there was an overlap of younger and older piglets with no opportunity to clean and disinfect the facility. A repeatable pattern emerged; the first few litters were asymptomatic and showed a satisfactory weight gain. However, by the time the eighth litter was introduced (after 5 weeks of continuous operation), a mild diarrhea was noticed in older piglets. With subsequent litters more severe illness, including vomiting, occurred; and after 9 weeks of operations, 50% died of gastroenteritis. At this time all piglets were removed so that the nursery could be

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cleaned and the first litter of piglets entered 1 week later. The same pattern of illness emerged but was subsequently prevented by a thorough cleaning of the facility before the introduction of a new litter.

During outbreaks of diarrhea in day care centers, fecal coliforms are recovered significantly more frequently from classroom objects, including water taps, than during nonepidemic periods, but the role in transmission is unknown (153, 154). Persistence of *Salmonella* sp. in the inanimate environment for more than 1 week has been documented (324).

The spread of rotavirus among hospitalized patients and to children admitted to rooms previously occupied by infected patients suggests that a contaminated environment may be a factor in viral dissemination (296, 298, 306). The massive number of rotavirus particles commonly seen in feces of infected children could easily cause environmental contamination. Persistence of excretion to the ninth day of illness and beyond would provide ample opportunity for such contamination. In most young infants, there is either no demonstrable rotavirus at the time of cessation of diarrhea, or significantly less; older children, on the other hand, have higher titers persisting after diarrhea ceases (285). This refers to virus detectable by electron microscopy, a method which is probably much less sensitive than culture (142).

The respiratory route may be important in transmission of viral enteric pathogens, and recent work has shown that rotavirus can survive in the airborne state for several days (325). In a study of children hospitalized with pneumonia, the rotavirus was recovered from respiratory tract secretions from four patients, and in two patients for whom paired sera were available, the presence of antibody rises suggests that it may on occasion be associated with pneumonia (326). The potential for respiratory transmission requires further clarification but has been suspected in outbreaks (327, 328). Alternatively massive environmental contamination with virus and a low infecting dose could explain the transmission which mimics airborne transmission. The role of contamination of the environment in the spread of bacterial pathogens is less clearly understood.

Morbidity and Mortality. Patients with metabolic diseases are less able to handle problems in fluid balance associated with the tremendous fluid losses which may accompany any diarrhea, but particularly rotavirus. Bone marrow transplant recipients who acquired diarrhea had a higher mortality rate (56%) than those who did not (13%) (123).

Control and Management. A strictly monitored hand washing program after toilet activities and before eating/feeding resulted in a 50% decrease in the entire 35-week study period in two day care centers compared to two noninterventions centers (329). A similarly dramatic impact of a hand washing program on intrafamily transmission of diarrhea was demonstrated in Bangladesh (330). Current methods of control are included in Table 28.12 (280,331). Other methods of control have been described (332). An effective vaccine is ultimately required (333). Additional therapy for bacterial diarrhea is described below.

Bacterial Diarrhea

Clostridium sp. C. difficile is commonly found in the stools of normal children, being present in 33% of children less than 1 year of age, 10% of children between 1 and 2 years of age, and very rarely between 3 and 10 years of age (334–336). It has been found more frequently in children with diarrhea during day care center outbreaks (57%) compared to those without diarrhea (9%) (337). Nosocomial pediatric disease has not yet been described. *C. perfringens* from an unidentified food source has been implicated in a large nosocomial outbreak involving 61 patients including children (338).

Cryptosporidium sp. Person-to-person transmission has been suggested in 4 cases involving pediatric patients and hospital staff, although a common earlier source and other exposure was not been ruled out (339, 340). The identification of *Cryptosporidium* in 65% of symptomatic children in a day care center compared to 10% of controls suggests that epidemic disease in immunocompetent children can occur (341). Additional day care outbreaks continue to be described (342) and with improved diagnostic efforts may well be identified in hospitals around the world (343).

Salmonella sp. and E. coli. Outbreaks are listed in Table 28.13. The association of antibiotic therapy with colonization by multiresistant *Salmonella* and the proneness of young children to develop systemic disease have been noted (307, 308, 312). While common source outbreaks have been described (309), transmission has generally been related to hand carriage, serious patient overcrowding, suboptimal nursery facilities, poor architectural design, and contamination of the

environment as in the adult. Children in the first year of life have increased attack rates of bacteremia and death with *Salmonella* and chronic disease and death with enteropathogenic *E. coli* (343, 344, 345).

Antibiotic therapy to reduce stool carriage and thereby minimize the reservoir is controversial (307, 346). Stool cultures for *Salmonella* sp. have continued to be positive, and there is probably no indication for suppressive therapy. On the other hand, suppressive therapy for enteropathogenic *E. coli* may be worthwhile in the hospitalized child.

Shigella sp. An outbreak of shigellosis in pediatric staff has followed contamination of tuna salad in a hospital salad bar. Fifty-one percent of staff were colonized but no patient illness occurred, although the hospital was closed to new admissions for 3 days (347). Appropriate antibiotic treatment rapidly eliminates shigella from the stool. Therefore treatment of all infected children regardless of severity of disease is recommended because of the high degree of contagiousness of shigellosis (344).

V. cholerae. Prophylactic antibiotic therapy may be of value (290).

Other. There have been no reports of nosocomial giardiasis or *Campylobacter* sp. to date.

Morbidity, Mortality, and Cost

Deaths directly attributable to nosocomial gastroenteritis infection have generally been caused by *Salmonella* infection (3, 233, 310, 312, 346). One estimate found the cost of reovirus diarrhea to be a prolongation of stay of 2.8 days at a cost of $836/infection (296). The indirect costs to the health care system (e.g., refusal of emergency admissions and curtailing of elective admissions) and to the family are unknown (310). Reduction of cholera spread through cross-infection in the children's infectious disease ward was said to reduce the number of cases in the hospital and the whole city drastically (290).

Previously Common Childhood Diseases

Pertussis

Following the introduction of pertussis vaccine, there has been a steady decline in the incidence of the disease. There are now 5 to 20 people dying of pertussis each year in the U.S., and the disease has been reduced to 1000 to 2000 cases a year. There is now an increasing incidence in many areas of the U.S. (348); the agent is exquisitely contagious with 100% of unvaccinated and 46% of vaccinated household contacts acquiring infection. Nearly half of the cases may be asymptomatic, and their role in transmission is unknown (349). Age does offer protection with 81% of contacts less than 1 year of age developing pertussis compared to 8% of contacts older than 20 years. Similarly, a history of immunization offers some protection, with pertussis developing in 30% of those immunized compared with 82% of those not immunized. The vaccine efficacy rate was estimated at 63%. In one series, 9 of 10 asymptomatically infected children had received three or more DTP immunizations (350). Serologic response in asymptomatic infections suggests that this exposure may be important in maintaining immunity. Pertussis occurs in adults, even in those with a history of previous infection or immunization. Illness in adults is generally less severe and may be misdiagnosed as bronchitis or an upper respiratory tract infection unless paroxysmal symptoms develop. The relationship of symptoms to increasing age, immunization, or previous infection has not been carefully studied (351, 352).

Hospital staff have transmitted this disease in three outbreaks (193, 194)—one in 1969 involving 11 adults (staff and their contacts) in Denver (193), another in 1974 involving 135 staff members and spouses and 6 patients in Cincinnati (194). Disease appears to have been spread to another patient after his exposure to the index patient from day 8 to day 10 of erythromycin therapy, although transmission by asymptomatic staff cannot be ruled out (353). Failure to recognize the disease in a mother and hospital staff with paroxysmal coughing with subsequent removal from duty has resulted in nosocomial disease (176).

Some data suggest that prophylactic erythromycin is effective in preventing colonization and disease in immunized and unimmunized contacts (176, 353–355). In a pertussis outbreak at Cincinnati Children's Hospital, clinical disease developed in five of five colonized contacts before prophylaxis was initiated. After beginning erythromycin prophylaxis, clinical pertussis developed in only one of eight colonized contacts (194). Erythromycin administered 5 days after exposure failed to prevent disease in a 5-month-old patient (353). Additional studies of the value of prophylactic erythromycin are needed but difficult to design because of the variable exposures before prophylaxis is initiated. Erythromycin is useful in eradication of the organism from cases; there are no reports of bacteriologic relapse in patients

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Table 28.17. Protoc

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* Modified from Mo
1:430–442, 1982.

Table 28.18. Contag

Disease
Measles
Mumps
Rubella
Pertussis
Varicella
Diphtheri

* Modified from Mc
1:430–442, 1982.

treated for 14 days, and most patients appear to be rendered noninfectious after 10 days (355, 356). Vaccination has been used in outbreak control in room and ward contacts less than 7 years of age and in older children and staff (194).

The protocol for management is found in Table 28.17 (see also Tables 28.18–28.21). Intervention includes the following:

Contacts less than 7 years old who were previously immunized against pertussis should receive a booster dose of vaccine, preferably as DTP, unless a booster dose was given within the past 6

Table 28.17. Protocol for Common Childhood Disease Exposure in Hospitalized Patients*

1. Isolate the contagious patient as defined in Table 28.18 and discharge if condition permits, especially if the patient has measles or chickenpox. If patient cannot be discharged, transfer to nearest isolation area, avoiding patient care areas during transport.
2. Delay admission to the exposed ward for an hour or so until the charts can be reviewed to determine who is susceptible.
3. Decide which patients were exposed to the disease. If the contagious patient used the play area, consider all other children using the play area to have been exposed. All other potential exposures in diagnostic facilities and operating room should be considered. Make a list of exposed patients. Determine their susceptibility as defined in Table 28.19. Private physicians should be notified if they have patients on the list, but the responsibility to isolate exposed susceptible patients who cannot be discharged should be clearly assigned to the pediatric representative on the hospital infection committee, nurse, or pediatric ward resident.
4. Identify high risk patients as defined in Table 28.20 who were exposed and require immediate prophylaxis as discussed in the text.
5. Discharge as many exposed susceptible patients as possible, before minimum of range of incubation period has elapsed since onset of exposure as defined in Table 28.21.
6. Move exposed susceptible who cannot be discharged before the time when a secondary case would be expected on the basis of the minimum of the incubation period. Put this exposed cohort under the proper isolation technique until after the maximum of range of incubation period as defined in Table 28.21.
7. Admit immune patients to floor without restrictions. Susceptible patients can be admitted provided the above precautions are followed carefully.
8. Decide which staff were exposed to the disease, including doctors, nurses, physiotherapists, radiology technicians, volunteers, students. Advise them of the need for prophylaxis or withdrawal from patient contact.

* Modified from Moffeth HL: Pediatric nosocomial infections in the community hospital. *Pediatr Infect Dis* 1:430–442, 1982.

Table 28.18. Contagious Period of Common Childhood Diseases*

Disease	Earliest	Latest
Measles	4 days prior to onset of rash	4 days after onset of rash
Mumps	1–2 days before parotid swelling	5 days after onset of parotid swelling
Rubella	Few days before rash	Few days after rash
Pertussis	Catarrhal stage	Rarely after fourth week of disease; 7–10 days after initiation of 10–14-day course of erythromycin
Varicella	48 hours before rash	5–7 days after onset of last vesicle
Diphtheria	Onset of illness	2–4 weeks; 1–2 days after initiation of penicillin therapy

* Modified from Moffet HL: Pediatric nosocomial infections in the community hospital. *Pediatr Infect Dis* 1:430–442, 1982.

months. Because immunity conferred by vaccine is not absolute, all immunized and unimmunized contacts should also receive erythromycin prophylactically (40 mg/kg/day for 10 days). Contacts not previously immunized should receive erythromycin for 10 days after the contact is broken; if it is not possible to break the contact, they should be treated for the duration of the cough in the index patient, or until the patient has received 7 days of treatment with erythromycin. Pertussis immune globulin (human) has shown no prophylactic effect in controlled trials (157). Ultimately, elimination of this disease, which has plagued patients and physicians for years (357), will depend on improved vaccine (358–360).

Table 28.19. Definitions of Susceptibility to Common Childhood Disease*

Measles	Those unable to provide documentation of (*a*) measles diagnosed by a physician (*b*) serologic confirmation of immunity, or (*c*) live measles vaccine on or after their first birthday.
Mumps	No practicable way of testing for susceptibility at the present time.
Rubella	Those unable to provide documentation of (*a*) serologic confirmation of immunity or (*b*) immunization.
Pertussis	No practicable way of testing for susceptibility at the present time.
Varicella	Those unable to provide documentation of (*a*) varicella diagnosed by a physician, (*b*) household exposure to varicella, or (*c*) serologic confirmation of immunity.

* Modified from Moffet HL: Pediatric nosocomial infections in the community hospital. *Pediatr Infect Dis* 1:430–442, 1982.

Table 28.20. Definitions of Patients at High Risk of Severe Disease from Common Childhood Diseases Who Require Special Intervention

Measles	All susceptibles
Mumps	None
Rubella	Suspect or confirmed pregnancy
Pertussis	Practically, all exposed
Diphtheria	Practically, all exposed
Varicella	Immunospressed patients (leukemia, lymphoma, congenital or acquired immunodeficiency, and recipients of 2 mg/kg/day of prednisone and other immunosuppressive treatment)
	Patients in plaster casts

Table 28.21. Incubation Period of Common Childhood Diseases*

Disease	Minimum (days)	Maximum (days)	Usual (days)
Measles	9	12	Same
Mumps	12	25	16–18
Rubella	14	21	16–18
Pertussis	7	14	7–10
Diphtheria	2	5 or longer	2–5
Varicella	10	21, 28 if VZIG given	10–14

* Modified from Moffet HL: Pediatric nosocomial infections in the community hospital. *Pediatr Infect Dis* 1:430–442, 1982.

Measles

Control of measles worldwide has met with variable success. Through a nationwide initiative to eliminate indigenous measles from the United States by October 1, 1982 through high immunization levels, aggressive surveillance, and vigorous response to cases, measles morbidity reached a new low of 3124 reported cases in 1981 (361). Young infants, susceptible adolescents, immigrants, and patients excluded from immunization for religious reasons continue to represent a potential risk to hospitalized patients. In 1980–1981, 205 cases were reported for an average of two importations/week with more than one-third of all importations from Mexico, Canada, and England and nearly one-quarter of cases associated with secondary transmission (160, 361). Nosocomial measles was reported more commonly than varicella, rubella, and mumps in hospital-wide surveillance berfore 1972 (10, 11, 13). Airborne transmission in doctors' offices has been documented (159. 160). In one report, a 7-month-old Korean orphan infected four other children. One had arrived 5 minutes before the patient left the office but had no face-to-face contact with her. The other three patients arrived 65 to 75 minues after the index patient had left.

Only one used the same examining room, but all four shared the waiting room. Survival of measles virus in droplet nuclei for over 2 hours has been documented in the laboratory (362).

The protocol for management is found in Table 28.17.

Intervention for susceptible children ≥ 1 year of age exposed for < 5 days includes immunization. Children during the first year of life should receive 0.25 ml/kg of immune serum globin (IG) and active immunization at 15 months. Susceptible older children exposed for more than 5 days should receive IG, then be actively immunized 3 months afterward. Immunocompromised children should receive 0.5 ml/kg of IG even if they were immune prior to the onset of immunosuppression. The maximal dose should not exceed 15 ml of IG (157, 363, 364).

Mumps

Investigation of patients on a children' tuberculosis ward exposed to mumps indicated that all susceptibles, as identified by neutralizing antibody test, acquired disease (over 25% asymptomatically) despite isolation at the first sign of parotid swelling. Mumps virus was recovered as early as 2 days before and as late as 6 days after the onset of parotitis (365). An epidemic of mumps occurred in patients in the children's orthopaedic division of an Alaskan hospital. The index case was believed to be a new staff nurse who had been visiting her nephew with mumps (197), suggesting a possible role for the asymptomatic carrier in transmission. ELISA screening may be of use in determining susceptibility, although vaccination of immune individuals is not associated with complications (366). The protocol for management is found in Table 28.17. Exposed susceptible children ≥ 12 months of age should be immunized (367, 368).

Rubella

The special problem of rubella is discussed in Chapters 12 and 13. Shedding of rubella in a 4½-year-old boy with congenital rubella has been documented (369). The protocol for management is found in Table 28.17. Susceptibles ≥ 12 months of age should be immunized unless they are of childbearing age. These patients require serologic testing and, if they are seronegative, appropriate follow-up (157).

Diphtheria

Outbreaks of diphtheria occurred at two centers for the mentally retarded. Eight children between 3 and 10 years of age developed nasal diphtheria and a ninth individual, a 21-year-old nursing aide, presented with the pharyngeal form of disease (198). The potential for an increased incidence of clinical diphtheria exists as carriage and disease continue to be reported in indigenous and immigrant populations (370). A protocol for management of exposed patients is shown in Table 28.17. The need for additional management, including diphtheria toxoid, antitoxin, and penicillin, must be determined by individual circumstances. All hospital contacts should be kept under surveillance for 7 days (157, 371).

Polio

Immunization programs have reduced the number of cases of paralytic poliomyelitis to 7 in 1981, although certain unimmunized religious groups continue to be at risk (372–376). No nosocomial disease has been described, although a nursery school outbreak has been reported (377).

Varicella-Zoster Virus Infection

Prevalence. Varicella presents a major problem in pediatric hospitals because of the possibility of airborne spread (35, 36, 378–381) without direct contact and the severity of illness that may occur in immunosuppressed patients (221, 382–387). In the U.S. 82% of varicella cases occur in the first 9 years of life, although in tropical areas varicella occurs at a later age, as is reflected in susceptibility of 4.5% of pregnant women from New York versus 16% of those from tropical areas (388–391) and severe nosocomial outbreaks in the tropics (378, 392).

Outbreaks. Outbreaks are listed in Table 28.22 (35, 36, 39, 195, 393). Twenty-eight cases of nosocomial varicella have occurred on wards despite the use of full isolation precautions for patients with varicella, including single rooms, closed doors, and prohibition of physical contact (35, 36, 39, 195). One outbreak was related in time to the vacuuming of the index patient's room, although varicella virus has not been successfully recovered from skin scales or fomites (195). Brief operating room exposure on the day before the onset of rash in an 8-year-old boy in the tropics resulted in disease in 12 medical and surgical staff (392). Three cases have occurred in leukemic toddlers confined to cribs 50 to 100 feet from the index case with leukemia and extensive varicella skin lesions (36). Disease has occurred in a patient on isolation precautions during the entire exposure and who was confined to a room on the same ward as an index case with varicella

Table 28.22. **Outbreaks of Nosocomial Varicella Infection on Pediatric Wards Reported in the Literature**

Reference	Disease in Index Case	No (%) of Cases in Susceptible Patient Contact	Susceptibility Test Used	Time Course
195	Varicella	8 (22%)	History, age	21 days
36	Varicella	3 (13%)	History	21 days
	Varicella	4 (24%)	History	21 days
35	Varicella	13 (54%)	History, FAMA	23 days
393	Zoster	3	History	31 days

pneumonia who was being ventilated (35). Furthermore, three isolated wardmates of a patient with zoster also acquired varicella (393). Disease has also occurred in a susceptible physiotherapist in Boston who did not have direct patient care with infected children (35). Seventeen presumed nosocomial cases have been identified only after discharge (35, 36).

In a period of 34 months, more than 500 hospital employees and 209 patients were exposed to varicella-zoster virus (VZV) following 22 uncontrolled hospital introductions. Five introductions by employees followed acquisition of varicella outside the hospital (394). Additional outbreaks have been investigated by the CDC, and many earlier reports can be found (10, 11, 13, 379, 380).

Mode of Transmission. Varicella can occur in a susceptible person exposed to either varicella or zoster. Because zoster is not associated with respiratory shedding of viral particles, except potentially when lesions involve the nose or oropharynx, infection is more likely to occur after exposure to varicella than zoster (395). The path of entry into the susceptible host is assumed to be the upper respiratory tract. The infecting dose has not been established. There are different strains of VZV identifiable by DNA fingerprinting, but it is not clear whether there is more than one serotype (221, 388). VZV chickenpox is transmissible at the time of the exanthem, although it cannot be isolated from the respiratory tract after the exanthem appears or immediately before the eruption even in the presence of vesicular lesions in the mouth possibly because the virus is inactivated by local factors or because the culture systems are insensitive (388, 389, 395). One of three children studied did transmit infection to a classmate the day before the appearance of the first skin lesion, similar to the previously mentioned tropical operating room exposure (392, 395). It is not known whether asymptomatic individuals carry the virus, although immune individuals can be asymptomatically infected as inferred by increases in antibody titers.

In spite of the relatively low infectivity of the virus on casual contact, transmission in an institutional environment occurs fairly readily. The thesis that airborne transmission of droplet nuclei, as well as contact infection, helps to spread the virus is supported by investigation of a hospital outbreak in which air-tracer studies of the movement of sulfur hexafluoride released in the room occupied by the index case clearly documented the preferential flow of air to adjacent rooms (35) with high occupant attack rates. A confirmatory report linked transmission of virus with the airflow from the isolation room to the corridor (195).

Susceptibility and Reinfection If an assessment of susceptibility is being made solely on historical information to assess immune status, the interview should be conducted by experienced personnel (394, 396) Susceptibility obtained through history may be unreliable. Eight percent of adults who said they had not had chickenpox developed infection after household exposure; 2% of those who were unsure of their history and 0.2% of those who said they had had the disease developed chickenpox under similar circumstances. The attack rate among children with a negative history in the same household was 95% (388). An attempt should be made to elicit a past history of exposure to siblings or children with varicella; persons with previous household exposure to active cases are likely to be immune. Individuals who have attended an urban school or had previous occupational exposure, e.g., in nursery school, kindergarten, or a pediatric health care setting, also are likely to be immune (396).

Susceptibility may be reliably determined by such sensitive and specific test as the fluorescent antibody membrane antigen test, immune adherence hemagglutination assay (IAHA), and

ELISA, but these tests are not yet widely available (397, 398). A skin test developed in Japan to detect susceptibility to varicella has also proven very sensitive (400) but currently lacks a commercial manufacturer and may not be sensitive in the elderly (389).

Increases in both humoral and cell-mediated immunity to VZV that occur in the majority of VZV-immune adults exposed to varicella suggest that subclinical reinfection does occur (401). Clinical reinfection can occur, both in immunocompetent and immunosuppressed individuals but appears to be unusual and mild (401, 402). An immunosuppressed patient with repeatedly positive VZV immunofluorescent antibody titers but no history of chickenpox developed varicella pneumonia (383). Twenty-eight percent of patients with preimmunization antibody to VZV experience a mild clinical illness, suggesting that these history-negative, seropositive patients remain at risk for VZV infection (401–405).

High Risk Patients. In immunosuppressed patients, such as those with Hodgkin's disease, non-Hodgkin's lymphoma, or lymphocytic leukemia, particularly those with absolute leukopenia, visceral involvement (pneumonia, hepatitis, encephalitis) may occur in 32% and death in 7% (382). In bone marrow transplant recipients after high dosage radiochemotherapy, infections are particularly severe. They are to be considered at risk regardless of their varicella history or the immune status of the donor. Cell-mediated immunity may be depressed for 100 days after transplant, and the level of depression correlates with increased susceptibility (405). Less drastic immunosuppression, such as that following organ transplant, also increases the risk (384). Defects in cell-mediated immunity appear to be associated with greatest risk. Patients on high dose steroid therapy, such as for rheumatic fever or the nephrotic syndrome, have more severe disease, whereas patients on low dose schedules are not at increased risk (385). Recipients of low doses of steroids, e.g., 5 to 10 mg of prednisone/day, do not exhibit increased morbidity when they develop varicella. A dose of prednisone equivalent to 2 mg/kg of body weight/day is arbitrarily considered to confer increased risk even in those with otherwise normal immune function (385). The effect of inhaled steroids or steroids applied topically to large areas of the skin is unknown (396). Patients receiving cytotoxic drugs are at increased risk in direct proportion to the degree of aggressiveness of the therapy (396).

Exposure. It is well recognized that continuing household exposure to chickenpox will result in infection in virtually 100% of susceptibles, but results of other types of exposure such as in hospitals are not predictable. In general, there is far less risk of transmission in these situations than following continuing household exposure, but in view of the high communicability, a liberal definition of exposure should be employed. A patient who has shared a hospital room containing four or fewer beds, or played for at least 1 hour with contagious children is said to have been exposed. Exposures may also occur in playrooms, X-ray department, and other locations in hospital (396).

Prevention: Varicella-Zoster Immune Globulin (VZIG)

VZIG can prevent chickenpox in exposed susceptible normal children. In a collaborative study in which 15 susceptible immunosuppressed children received zoster immune globulin (ZIG) within 3 days following exposure, there were no deaths and only one child developed progressive varicella, although a mortality rate of 7% and progressive disease in 30% were expected on the basis of previous studies at that time (386). Administration of zoster immune plasma 7 days after exposure did not prevent severe varicella from developing (383). Patients who develop 4-fold antibody rise from high titer ZIG have a significantly lower risk of death and complications (387). VZIG appears to offer protection for 3 to 4 weeks after administration. Patients receiving intravenous immune serum globulin every 4 weeks do maintain titers comparable to those patients receiving VZIG every 3 weeks. Because higher titers are achieved sooner after administration of intravenous immune serum globulin, it might be especially useful in patients receiving prophylaxis more than 4 days after exposure (407). VZIG can prolong the incubation period for up to 28 days, so exposed recipients who remain in hospital must be isolated for 10 to 28 days postexposure (396).

Vaccine. The vaccine, first available in Japan, is a live virus vaccine attenuated by multiple passage in cell culture capable of inducing immunity to varicella-zoster virus in a high percentage of normal (404) and immunocompromised (408–411) children. In a study by Gershon et al (409), over 90% of 191 study participants with leukemia showed an immune response after receiving two doses of vaccine. Eighty percent of leukemia vaccinees with subsequent household

exposure have remained free of illness; the other 20% had a mild disease with about 50 vesicular lesions. The 4 of 22 patients exposed who did develop chickenpox acquired milder disease than might be expected in healthy children exposed to varicella. The attack rate of 18% was significantly lower than the 80 to 90% usually seen in healthy children with household exposure. Similar success has been documented in other patients with lymphoreticular malignancies, although 2 patients who had failed to develop significant lymphocyte stimulation to VZV antigen after immunization developed a blastogenic response on re-exposure. One household contact seroconverted, presumably due to the vaccine strain (412). This vaccine is unlikely to be recommended for normal children in the near future, since extensive studies will be needed to evaluate the potential risk of delaying natural infection (410, 411). Reinfection and latent infection appear to follow vaccination of immunosuppressed children just as they may follow natural infection. Normal children appear to acquire complete protection. Vaccine has been administered to 11 children before or immediately after exposure to a child with zoster who infected three cases of the ward contacts (393). Although all showed an antibody response, additional studies are needed to determine the safety of this procedure.

Control and Management

Management is summarized in Table 28.23 (396, 406, 413–415). Isolation of patients who have received vaccine, who may develop mild disease, is recommended because of the theoretical risk to ward patients based on secondary attack rates in households. Casual management on the wards is costly (416).

Pre-employment serologic or skin testing and varicella immunization would reduce the cost and turmoil of occupational exposure (394) but may not be necessary. To protect a semiclosed community against varicella adequately, all infants less than 6 months old may require immunization. The incidence of varicella has not been decreased in an institution using the vaccine since 1975, although the average rate of immune individuals in the population was maintained at more than 70%. Varicella outbreaks continued to occur, including children less than 6 months of age (417).

Invasive Bacterial Disease

H. influenzae

H. influenzae is transmitted by person-to-person contact via infected droplets of respiratory tract secretions. The respiratory tract is the portal of entry in cases of meningitis, and the upper respiratory tract remains colonized until effective antibiotic therapy has been instituted. Only one case of nosocomial disease has been described (418). A 4-month-old boy undergoing repeated subdural taps was hospitalized in the same room as a 4-month-old girl with *H. influenzae* osteomyelitis and septic arthritis who had received four doses of ampicillin, four doses of chloramphenicol, and three doses of oxacillin intravenously 24 hours and 50 minutes prior to his admission to that room. At day 11 of hospitalization, he developed meningitis with the strain of *H. influenzae* which had the same outer membrane protein profile as the index case (419). Lipopolysaccharide subtype may be used to distinguish some strains not differentiated by outer membrane protein (420). Two nosocomial cases occurred in a chronic care facility for the retarded in which 11% of the staff and 18% of the patients were

Table 28.23. Management of Nosocomial Varicella

1. Patients with varicella should be discharged if possible.
2. Patients with varicella who cannot be discharged should be placed under strict isolation or cohorted with other patients who have varicella in the same room.
3. Exposed susceptibles should be discharged as soon as possible.
4. Exposed susceptibles who cannot be discharged should be placed on strict isolation for 10 days after the first possible exposure to 21 days after the last possible exposure.
5. Exposed susceptibles at high risk should receive zoster immune globlin or varicella-zoster immune globulin and isolated for 10 to 28 days after the first and last exposures, respectively. It appears beneficial to discontinue chemotherapy or radiotherapy, if possible.
6. Exclude susceptible immunocompromised patients from admission to that ward.
7. Susceptible staff should not be allowed to work with patients with varicella-zoster infections, and a sign stating this may be placed on the door.
8. Susceptible staff, once exposed, should not be allowed to work with high risk patients from 10 days after the first possible exposure to 21 days after the last possible exposure.

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colonized (129). Respiratory isolation is recommended until patients have completed 24 hours of treatment with ampicillin or chloramphenicol and theoretically until nasopharyngeal eradication of the organism has been achieved. The infected patient should receive rifampin prophylaxis, 20 mg/kg (600 mg maximum dose), given once daily for 4 days and usually initiated just prior to discharge from the hospital (421). Recently simultaneous administration of chloramphenicol and rifampin has been associated with subtherapeutic chloramphenicol levels, and this administration requires critical evaluation before a recommendation can be made. Rifampin can induce hepatic microsomal enzymes, and possibly its administration should be deferred until chloramphenicol administration is complete (422). Day care contacts should be managed according to local public health policy (423). If there are additional family members < 4 years of age or immunosuppressed children of any age in the family (157, 225), the entire family should be counseled. Vaccine is close to licensure and may be recommended for use in exposed 18- to 47-month-old children (424).

N. meningitidis

No nosocomial cases have been reported in the pediatric population (425, 426), although six cases occurred in children situated 100 cm nose-to-nose from the index case during a 6-day classroom epidemic (427, 428). The exposed patient should receive rifampin prophylaxis, 20 mg/kg (divided every 12 hours for 2 days), or sulfonamides if the strain is sensitive (157). Vaccine may be of use in outbreaks involving types a or c meningococcus (428).

S. pneumoniae

S. pneumoniae is presumably transmitted by person-to-person contact via infected droplets of respiratory tract secretions, but the low pathogenicity in the normal child precludes the need for prophylaxis.

Group A Streptococcus

Transmission of group A streptococcus on pediatric wards appears to be rare now, although children with the early phase of pharyngitis are effective disseminators of the agent. Outbreaks regularly occurred in rheumatic fever units prior to the availability of penicillin (429, 430). A 6-month-old infant with an infection of the skin superimposed on infantile eczema contaminated the ward environment (air, dust, and bed clothes). Twenty-five infants and 18 adults, including attending staff and visitors, developed infections (431). Therapeutic and prophylactic penicillin was recommended for control. When secondary cases are occurring, the environment is probably heavily contaminated (429–431). In detention centers and jails outbreaks have been controlled through identification and treatment of all cases plus environmental cleaning (432). A 10 day course of penicillin therapy for all entrants to an institution may be necessary (429–432). Foodborne outbreaks are more likely to be self-limiting (430).

S. aureus

An outbreak in a pediatric residental facility was controlled with the introduction of a relatively benign strain of *S. aureus* 502A following the failure of routine infection control measures (434).

Multiply Resistant Organisms

S. pneumoniae has been associated with nosocomial disease and death in pediatric patients in South Africa (88). In the day care center attended by an infected child, 27% of children, particularly those with a history of antibiotic use, were colonized (435).

Methicillin-resistant *S. aureus* and other multiply resistant organisms are very difficult to control once introduced (436) and may colonize patients for months following discharge. The CDC guidelines should be followed (166).

Fever

Device-related infections, influenza A and other intercurrent viral infections including echovirus, rhinovirus, coxsackie B, parainfluenza 3 and herpes simplex (255, 437–439), and endotoxemia (44) may present with fever. Presumed endotoxemia developed in two pediatric patients receiving total parenteral nutrition contaminated with endotoxin. A combination of equipment inadequacies, including failure to disassemble and sterilize a bypass valve and pressure gauge after bulk preparation of solution, and faulty laboratory testing in which the standard USP rabbit test for endotoxin was being performed with only one-tenth of the required solution, resulted in a slowly increasing level of pyrogen contamination which remained undetected until clinically significant pyrogen reactions occurred.

Cutaneous and Other Fungal Infections Originating in Hospital

Rhizopus sp.

Contaminated elastic bandages (Elastoplast) applied to a buttock abcess in a 7-year-old boy and the biopsy site of a 6-year-old girl both with lymphoblastic leukemia led to deep abscesses caused by *Rhizopus oryzae* which were successfully treated with topical and parenteral amphotericin B and surgical debridement (441, 442).

Aspergillosis sp.

Hospital renovations, particularly those resulting in a disturbance of dust in the false ceilings and problems with air handling systems, can lead to nosocomial aspergillosis of the skin and subcutaneous tissue, paranasal sinuses, and lungs in immunocompromised children, including those who have had bone marrow transplant (224). Disease occasionally occurs in immunocompetent children (443). Three children with hematologic disorders developed *A. flavus* infections at the point of contact with a paper-covered board or adhesive tape used to immobilize the extremity during intravenous therapy for 5, 7, and 14 days, respectively (234). The initial lesion was an erythematous papule which progressed to an ulcer with a central black necrotic eschar. All died, and in two the cause of death was overwhelming fungal infection. Cross-circulation as a result of air backflow through a common duct during an exhaust for shutdown was temporally related to pulmonary, sinus, and periorbital infections in five patients with acute leukemia (222). The introduction of routine cleaning procedures for air conditioning equipment and rooms was followed by only two cases in the next 12 months. A 2-year-old patient died of disseminated *A. fumigatus* following repair of a tetralogy of Fallot. Although the source was not proven, the event was associated with hospital construction and a pigeon roost on an air conditioner outside of the operating room (444). Environmental review is recommended at the time of a case of *Aspergillus* endocarditis because of the likelihood of airborne inoculation of the heart during operation (444). In other cases, no environmental source has been recognized. Early diagnosis requires prompt biopsy of any new lesion. Serology while specific is not sensitive, and the value of surveillance, cultures, and prophylactic antifungal therapy is unclear (445, 446). Prevention and control measures have included the following: establishing impervious barriers between patients and construction areas to prevent dissemination of dust, cleaning renovated areas well before occupancy, moving high risk immunosuppressed patients from adjacent and lower floors to an area of the hospital not under construction, installing dampers to isolate airflow to each unit, vacuuming false ceilings and ventilation ducts; disinfecting air ducts and removing and replacing high efficiency, particulate air filters. Intensive air filtration in the rooms of high risk patients may be of value.

Miscellaneous Infections

Legionnaire's Disease

L. pneumophilia infection appears to be fairly common subclinical or minor infection in early life with detectable antibody titers in many school-aged children (447–449). Very rarely it is associated with pneumonia in children (450–453). Almost all pediatric cases have occurred in severely immunodeficient children (450–454). Fatal nosocomial disease is extremely rare but did develop in a 13-year-old girl following bone marrow transplantation. Prevention and control of the infection have recently been reviewed and are discussed in Chapter 20 (455, 456).

Hepatitis A

Hepatitis A infections in hospitals are generally the result of transmission from clinically anicteric patients with fecal incontinence who are in the prodromal phase of illness when the diagnosis is not suspected (236, 457–462). These are summarized in Table 28.24. Most cases occur in staff; nosocomial disease in children is rarely documented (236). Levels of virus in stool are usually at their highest at or before elevated levels of liver enzymes occur (235), although fecal shedding can continue until at least 2 weeks after the onset of dark urine (463). The virus may survive drying for more than 1 month. Failure to isolate a patient with explosive diarrhea in whom hepatitis A (235, 236, 457) was ultimately diagnosed has resulted in additional cases in staff and patients (236, 457). Staff in contact with two patients on enteric precautions (457, 458) acquired the infection. Hematologic transmission has been postulated following the occurrence of hepatitis A in a baby who received blood from a man who developed hepatitis A 28 days after donating blood (460).

Although attack rates are generally higher in nurses who presumably have prolonged patient contact (25% of susceptibles) (459), disease has

Table 28.24. Outbrea in the Literature*

Reference
457
458
461
460
459
236

* From Krober MS, B for spread. *Pediatr Infect*

Table 28.25. Attack

Position
Physicians
Nurses
Nursing assistants
Medical students
Other exposed person
Total

* From Krober MS, B for spread. *Pediatr Infect*
† Includes intensive ca

been reported in an in "a scrupulous hand w at the bedside (458). T may be less common susceptibles to hepati

...ems and construction ...tion of dust, cleaning ...ire occupancy, moving ...sed patients from adja... area of the hospital ...installing dampers to ...vacuuming false ceil... ...ducting air ducts ...high efficiency, par... ...air filtration in the ...s may be of value.

...s Infections

...s Disease

...appears to be fairly ...ter infection in early ...body titers in many ...449). Very rarely it is ...ia in children (450–... cases have occurred in ...children (450–454). ...extremely rare but ...old girl following bone ...vention and control ...ly been reviewed and ...0 (455, 456).

...s A

...hospitals are generally ...rom clinically anicteric ...fluence who are in the ...when the diagnosis is ...462). These are sum... ...ases occur in staff; ...dom is rarely docu... ...in stool are usually ...ated levels of liver ...gh fecal shedding can ...eeks after the onset of ...s may survive drying ...ure to isolate a patient ...from hepatitis A (235, ...diagnosed has resulted ...d patients (236, 457). ...atients on enteric pre... ...ed the infection. He... ...ther postulated fol... ...hepatitis A in a baby ...mom who developed ...ating blood (460). ...is generally higher in ...ve prolonged patient ...es) (459). disease has

Table 28.24. Outbreaks of Hepatitis A among Pediatric Hospital Personnel and Patients Reported in the Literature*

Reference	Index Patient	Total No. of Secondary Cases	Attack Rate
457	18-month-old boy with shigellosis	14	20
458	21-month-old child with Down's syndrome, amebic liver abscess, and dysentry	4	3
461	23-month-old child with Down's syndrome and congenital heart disease	4	Unknown
460	1-month-old girl with osteomyelitis	10	Unknown
459	34-month-old girl with Down's syndrome and colostomy for imperforate anus	8	10 (12% of susceptibles)
236	1-year-old girl with congenital heart disease	19	18.5 (12% of susceptibles)

* From Krober MS, Bass JW, Brown JD, Lemon SM, Rupert KJ: Hospital outbreak of hepatitis A: risk factors for spread. *Pediatr Infect Dis* 3:296–299, 1984.

Table 28.25. Attack Rate for Exposed Susceptible Hospital Personnel Reported in the Literature*

Position	No. Exposed	Blood Samples Obtained	Susceptible (IgG Antibody-Negative)	No. of Cases of Hepatitis	Attack Rate (% of Susceptibles)
Physicians	11	11	10	1	10
Nurses	11	16	16	4	25
Nursing assistants	29	28	20	3	15
Medical students	4	4	4	0	0
Other exposed personnel†	25	22	18	0	0
Total	80	81	68	8	12

* From Krober MS, Bass JW, Brown JD, Lemon SM, Rupert KJ: Hospital outbreak of hepatitis A: risk factors for spread. *Pediatr Infect Dis* 3:296–299, 1984.

† Includes intensive care unit, operating room, catheterization laboratory, and pulmonary service personnel.

been reported in an infectious disease consultant, "a scrupulous hand washer" who stayed 1 hour at the bedside (458). Transmission among adults may be less common in view of the failure of 21 susceptibles to hepatitis A virus to acquire the infection from continent adults (462, 464). Attack rates are given in Table 28.25.

When hepatitis A is diagnosed in a child who is found retrospectively to have had diarrhea during hospitalization before the diagnosis of hepa-

titis is made, immune serum globulin, 0.02 ml/kg, might be of use in hospital personnel exposed during the period of diarrhea provided that less than 2 weeks have elapsed (157, 235, 458). The risk of transmission appears to be greater if the index case is young, mentally retarded, or fecally incontinent.

Hepatitis B

Although high rates of infection are found among homosexuals, patients on chronic hemodialysis, intravenous drug abusers, those of Asian descent, and those receiving frequent blood transfusion (157), there is a paucity of data on the incidence of hepatitis B in pediatric institutions. In one pediatric hemodialysis unit, 58% of the patients had at least one positive hepatitis B surface antigen (HBsAg) determination (465). Vaccine administration was effective in preventing hepatitis in 10 children with chronic renal failure who were immunized and followed for 16 to 33 months (466). The prevalence in pediatric oncology units has varied from 20% of patients by radioimmunoassay (RIA) (HBsAg) and 8% of DNA (anti-HBs) (467) in one center to 1% by RIA (HBsAg), 10% RIA (anti-HBs), and 7% (anti-HBc) (468) in another center. This may be explained by "third generation" testing through RIA and reversed passive hemagglutination techniques and the exclusive use of blood and blood products from volunteer blood donors in the second study. In the second study the prevalence was higher among those receiving chemotherapy (19%) than among those not receiving chemotherapy (7%).

Horizontal, non-parenteral transmission of hepatitis B virus via the exchange among children of objects contaminated with oral secretions such as chewing gum was the explanation given for 15 cases among 21 people in two families (470). Human biting was recognized as a probable mode of transmission in an outbreak in a residential institution for the mentally retarded (471). Both of these methods in addition to the traditional parenteral route may be important in a pediatric hospital. Classroom transmission to students sharing a room with mentally retarded chronic hepatitis B carriers appears to be low (1.8%) in a facility with a strong continuing health education program. These results should not be extrapolated to the residential setting (472). Infants born to carrier mothers who do not receive currently recommended prophylaxis (473) will continue to provide a reservoir of the virus if basic infection control measures are not followed.

In one Canadian pediatric hospital 28.3% of foreign-born, high risk staff but only 2.7% of north American-born, high risk personnel were anti-HBs-positive (191). This may be an underestimation of the problem because the nature of the screening was not stated and only one marker was included. The recommendations for the use of hepatitis B vaccine are currently under review. Adequate environmental disinfection is important (152). The risk to pediatric health care personnel may not be as high as that reflected in adult studies (474, 475) and is discussed in Chapters 12 and 13.

Non-A, Non-B Hepatitis

During two nosocomial outbreaks of non-A, and non-B hepatitis in a cardiovascular surgical unit in Japan, the incidence of 21.8% in the population between 1 and 19 years of age was lower than the 43% incidence observed in adults (476).

Cytomegalovirus Infections

The hazard of transfusion-related CMV infection and employee health-related issues are described elsewhere. Studies of CMV have found infection rates for preschool-aged children in the U.S. to range from 5 to 30% with early acquisition more common among children of lower socioeconomic status (477). Childrearing practices can greatly influence the incidence of infection so that in populations from New Guinea, the Hebrides, and kibbutzim in Israel, the rates are very high. Fifty-seven percent of children enrolled in group day care have been found to shed CMV in the urine, significantly more than either the rate of viruria or seropositivity among children in home care (478). Children less than 12 months of age at enrollment to this study had an increase in saliva excretion or viruria from 10% at entry to more than 80% 1 year later. While the incidence of nosocomial acquisition in pediatric facilities outside of the nursery is unknown, the potential for transmission through routes other than blood may be great depending on the population hospitalized, and ultimately immunization is desirable (479, 480).

The value of gown and mask isolation procedures in children with leukemia was studied during a 22-month period. The infection rate in the 13 months following the introduction of isolation was not associated with a decreased incidence of infection in the immunocompromised host (481, 482), supporting the importance of other modes

of transmission now known to include blood (483, 484).

Acquired Immunodeficiency Syndrome (AIDS)

Of 35 children with AIDS there have now been six reported whose sole risk factor for AIDS was receipt of blood transfusions (485, 486). Two boys, aged 7 and 10 years, with severe hemophilia A have developed immunodeficiency, presumably secondary to treatment with factor VIII concentrate (487). The prevalence of AIDS among hemophiliacs is currently under study (488). Although secondary cases have not been observed among medical personnel caring for patients with AIDS, current precautions are recommended for all patients with newly recognized severe cellular immunodeficiency and opportunistic infection, pending exclusion of AIDS (489).

Scabies

The prevalence of scabies varies among preschool and young school-age children. Sexually active adolescents are at risk of acquiring scabies. The failure to observe the mite (*Sarcoptes scabiei* var. *hominis*) without magnification contributes to the increased risk of secondary transmission to staff and tertiary transmission to other patients or residents. Primary intimate contact with an infected person is probably required, although fomite transmission may be significant, particularly for Norwegian scabies which can survive for 2 to 3 days off the skin surface (490). Patients with persistent pruritus with or without extensive crusting or scaling of skin require confirmatory skin scraping (196). If scrapings from two or more patients are positive and if one or more staff members exhibit pruritus or show positive scrapings, it is necessary to administer simultaneous mass treatment or prophylaxis. However, personnel with little direct patient contact (e.g., housekeepers) may be omitted. Sensitivity to the emotional needs of personnel is essential. If scabies is identified in patients or staff, post-treatment surveillance is essential because active infestations may occur 1 to 3 months after apparently successful treatment (196, 490–492). Treatment protocols should be readily available on all wards for use 24 hours a day.

Parvovirus

A report of nosocomial parvovirus infection follows reports of an association between serum parvovirus-like virus and bone marrow aplasia. A 12-year-old patient with sickle cell anemia who became severely anemic with absent reticulocytes seroconverted to parvovirus between 9 and 11 days after contact in hospital with a 4-year-old girl who had serologic evidence of a recent parvovirus infection (493). The mode of transmission of this agent and the true incidence of infection are unknown (494).

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