Through A Glass Darkly

Nosocomial Pseudoepidemics and Pseudobacteremias

Appearances to the mind are of four kinds. Things either are what they appear to be, or they neither are, and do not appear to be; or they are, and do not appear to be; or they are not, yet appear to be. Rightly to aim in all these cases is the wise man's task.

ERACUTUS

The experience recounted by Lynch and his co-workers in this issue of the Archives (see p 65) epitomizes two phenomena that are being encountered with increasing frequency by present-day hospital epidemiologists, "pseudoepidemics" and "pseudoinfections."

A pseudoepidemic of nosocomial infections is the occurrence of an increased number of infections in the hospital, usually caused by one species, that is misconstrued as denoting a true epidemic. Recognizing a nosocomial epidemic—which, believe it or not, can often be exceedingly difficult if it is caused by a common pathogen or smoldering on over a prolonged period—is predicated on knowing the expected or baseline (endemic) rate of nosocomial infection caused by the putative epidemic pathogen. Pseudoepidemics usually derive either from inadequate baseline data or even a total lack of such data (ie, no mechanism for surveillance of nosocomial infections or failure to even attempt to acquire baseline data retrospectively, usually possible and certainly acceptable epidemiologically) or from misinterpreting clinical or microbiologic data as representing infection, ie, pseudoinfections.

Pseudoepidemics of nosocomial infections, or epidemics of pseudoinfections, seem to be one of our many maladies of medical progress, reflecting intensifying interest in nosocomial infections and the increasing complexity of diagnostic clinical microbiology. Pseudoepidemics of all types comprised 11% of 181 nosocomial outbreaks investigated by the Center for Disease Control, Atlanta, between 1966 and 1975. I am aware of at least 11 well-proven reports of epidemic pseudobacteremia alone in the modern medical literature (Table); all took place since 1968 and six of them since 1974.

Allowing for an expected 3% to 5% rate of false-positive blood cultures due to contaminants introduced during drawing the specimens or processing them in the laboratory, if multiple blood cultures are drawn carefully, the diagnosis of bacteremic infection is probably the most objective of all infections encountered in clinical medicine, because recovery of any microorganism from one or more cultures of blood is clearly abnormal and, until proved otherwise, must be regarded as representing possible septicemia. Guidelines for interpreting positive blood cultures and discriminating between sporadic contaminants and true bacteremia have been developed, based primarily on the number of cultures that are positive and the nature of the isolate—whether it is a "common contaminant" such as Corynebacterium sp or Bacillus sp or is a species that virtually always is a true pathogen, such as Streptococcus pneumoniae, Neisseria meningitidis, or Bacteroides fragilis. But here is the crux: the extreme sensitivity of blood culture systems renders them susceptible not only to occasional sporadic contamination, but in the right circumstances, to contamination of a large number of cultures, producing a cluster of pseudobacteremias. If contamination is with a plausable pathogen such as a Gram-negative bacillus (eight of the reported 11 outbreaks), it is easy to see why true infection and even a true epidemic are logically assumed.

Pseudobacteremias can in theory derive from contamination introduced at any stage, from drawing the cultures at the bedside to processing them in the laboratory (Table). Clusters of pseudobacteremia that became pseudoepidemics have been traced to extrinsically contaminated antiseptics (aqueous solutions of benzalkonium chloride or chlorhexidine) used to disinfect patients' skin prior to drawing the cultures; cross-contamination of blood cultures by microorganisms in nonsterile evacuated blood-collection tubes filled with the same syringe prior to inoculating the blood cultures; contaminated holders used with evacuated blood-collection tubes; heavy environmental contamination, including of patients' skin and blood-drawers' hands, caused by large numbers of airborne microorganisms in pediatric mist tents; contaminated penicillinase added to blood cultures in the laboratory; intrinsic (manufacturer-related) contamination of a commercial blood culture medium; cross-contamination of blood cultures being processed by automated (radiometric) techniques because the sampling probe did not self-caterize properly; a laboratory technician who was processing blood cultures and turned out to be a carrier and, presumably, a heavy shedder of Staphylococcus aureus; and most recently, as shown by Lynch and co-workers, contaminated tincture of thimerosal used to disinfect the diaphragms of blood culture bottles in the laboratory. Several of these outbreaks involved intrinsic contamination of a nationally distributed product (blood-collection tubes, blood culture media), resulting in epidemic pseudobacteremias in multiple hospitals in different states, and thus assumed national scope.

Prompt identification and confirmation of pseudobacteremia is obviously very important; patients may unnecessarily be treated with potentially toxic antibiotics; true bacteremia may be concealed by overgrowth of the contaminated species in the blood culture; the positive blood cultures may prevent or delay further search for the cause of patients' fevers or other symptoms that prompted blood culturing in the first place; and the circumstances resulting in pseudobacteremia may have the potential of also causing true iatrogenic bacteremia. eg, microorganisms from contaminated blood collection tubes refluxing directly into the patient's bloodstream.

Recognizing and establishing rapidly that an increased frequency of positive blood cultures represents contamination on a large scale, and thus epidemic pseudobacteremia, can be difficult as exemplified by the fact that of the 11 reported experiences, the median length of time that pseudobacteremias had been occurring in the hospital before they were conclusively identified was six months (Table); in four instances, it took ten months to two years and the occurrence of as many as 79 pseudobacteremias before the situation was clarified and resolved. Further attesting to the insidiousness of pseudobacteremia, following the 1974 report of true bacteremias and the 1975 reports of pseudobacteremias traced to contaminants in commercially manufactured blood-collection tubes, it was shown by Washington that tubes obtained from hospitals across the United States contained viable microorganisms. Yet, only a handful of over 8,000 hospitals in this country and Canada using 500 million tubes annually ever identified and reported a problem with either pseudoinfections or bona fide bacteremias.

Epidemic pseudobacteremia should be strongly suspected in the following circumstances.

1. When a cluster of blood cultures is positive for a new
or "unusual" blood pathogen, eg, *Acinetobacter*, *Moraxella*, *Bacillus* sp, or a non-aeruginosa species of *Pseudomonas*.

2. When the affected patients do not consistently show signs or symptoms consistent with bloodstream infection (this may require a careful case-control analysis to establish).

3. When the putative epidemic bacteremias are "primary," ie, the bloodstream pathogen is not isolated from plausible sites of local infection such as surgical wounds or the urinary tract. However, it must also be kept in mind that primary nosocomial bacteremias frequently denote infusion-related sepsis.\(^1\)

4. When bacteremias are inexplicably high-grade (most or all of the blood cultures are positive), usually seen only with endovascular infections such as endocarditis.

With rare exceptions, investigation of possible pseudobacteremias or any potential nosocomial problem, for that matter, should include an early case-control study,\(^1\) as commendably done by Lynch et al, that compares exposures of putative epidemic cases and carefully selected control patients (usually randomly selected patients whose blood cultures, drawn during the same period as positive cases, were negative or, alternatively, were positive for other species). This analysis strives to identify significant differences in host or therapeutic factors—in the case of possible pseudobacteremias, differences in some aspect of drawing and processing blood cultures—that point toward the responsible factor or factors. Exposure of all or most cases, but none or relatively few of the control patients, to a factor or factors constitutes strong presumptive evidence implicating the factor(s) in the genesis of the problem. Microbiologic confirmation of the source of contamination ideally should only confirm what is already strongly suspected based on clinical-epidemiologic analyses.

In view of the increasing frequency of true epidemics of nosocomial bacteremia (86 reported outbreaks since 1965) and of pseudobacteremia (Table), it is obviously very important that all blood isolates be identified routinely through species by hospital laboratories and that complete antimicrobial susceptibility testing be performed on all blood isolates. The pattern of susceptibilities (antibiogram) is often an invaluable identifying marker and can be used as a presumptive means of subtyping isolates in a possible epidemic.\(^1\) An isolate from every bacteremia should ideally be saved for at least three to six months for future characterization if an epidemic should occur. Most importantly, infection control personnel and laboratory personnel should maintain a close and continuing dialogue. A cluster of isolates of one species from any site should be immediately reported to infection control personnel and the isolates retained for possible further analysis. If true infection or pseudoinfection is suspected to originate from intrinsic contamination of a commercial product, it becomes a matter of major public health concern: local and federal health authorities (the Food and Drug Administration and the Center for Disease Control) should be immediately informed and unmanipulated samples of the implicated product retained for analysis by these agencies.

Lynch and colleagues elected to resume the use of tincture of thimerosal (1:1,000 in a 43% alcohol solution) for disinfecting the diaphrags of blood culture bottles in their laboratory, despite the overt evidence of their experience showing that the agent is not reliably effective against certain environmental contaminants, such as *Clostridium*. Why? It was hypothesized, reasonably, that the agent became contaminated during use. Despite instituting precautions to guard against future in-use contamination, what guarantee is there that a bottle of "working" thimerosal will not again become contaminated, possibly by some other as yet undefined mechanism? In a survey of 20 US university hospital laboratories, I was unable to identify any that use thimerosal for decontaminating diaphrags of blood culture bottles; most use tincture of iodine or povidone-iodine and several use 70% alcohol.

Thimerosal is a weak and almost archaic disinfectant, clearly inferior even to alcohol alone used in optimal germicidal concentrations of 70% to 90%.\(^1\) While alcohol in such concentrations is an excellent intermediate-level germicide, it is also not sporicidal, and surgical infections

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**Reported Epidemics of Pseudobacteremia**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year (Duration)</th>
<th>Epidemic Microorganism</th>
<th>No. of Patients With Positive Cultures</th>
<th>Mechanism of Contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norden(^1)</td>
<td>1968 (5 days)</td>
<td><em>Escherichia coli</em></td>
<td>7</td>
<td>Contaminated penicillinase in multidose vial</td>
</tr>
<tr>
<td>Faris and Sarting(^2)</td>
<td>1970 (10 mo)</td>
<td><em>Mima polymorpha</em> (^3)</td>
<td>24</td>
<td>Contaminated penicillinase in multidose vial</td>
</tr>
<tr>
<td>DuClos et al(^1)</td>
<td>1973 (16 days)</td>
<td><em>Moraxella nonliquefaciens</em></td>
<td>8</td>
<td>Contaminated holders for evacuated blood-culture tubes</td>
</tr>
<tr>
<td>Noble and Reeves(^4)</td>
<td>1974 (2 mo)</td>
<td><em>Bacillus sp</em></td>
<td>44(\dagger)</td>
<td>Intrinsically contaminated blood-culture media</td>
</tr>
<tr>
<td>Kaslow et al(^5)</td>
<td>1971-1972 (12 mo)</td>
<td><em>Pseudomonas cepacia</em> or <em>Enterobacter</em> sp</td>
<td>79</td>
<td>Contaminated aqueous benzalkonium solution used for skin antisepsis</td>
</tr>
<tr>
<td>Coyle-Gilchrist et al(^6)</td>
<td>1973-1975 (24 mo)</td>
<td><em>Flavobacterium meningosepticum</em></td>
<td>6</td>
<td>Contaminated aqueous chlorhexidine solution used for disinfection</td>
</tr>
<tr>
<td>Hoffman et al(^7)</td>
<td>1975 (6 mo)</td>
<td><em>Serratia marcescens</em></td>
<td>45(\dagger)</td>
<td>Intrinsically contaminated evacuated blood-collection tubes</td>
</tr>
<tr>
<td>Semel et al(^8)</td>
<td>1975-1977 (17 mo)</td>
<td><em>Pseudomonas maltophilia</em></td>
<td>25(\dagger)</td>
<td>Heavy environmental contamination in pediatric mist tents</td>
</tr>
<tr>
<td>Snyder et al(^9)</td>
<td>1975-1976 (7 mo)</td>
<td><em>Acinetobacter calcoaceticus</em></td>
<td>11</td>
<td>Colonized laboratory technician who processed positive cultures</td>
</tr>
<tr>
<td>Dolan et al(^10)</td>
<td>1978 (4 days)</td>
<td><em>Staphylococcus aureus</em></td>
<td>11</td>
<td>Contaminated thimerosal solution used to disinfect diaphrags of blood culture bottles in laboratory</td>
</tr>
<tr>
<td>Lynch et al(^11)</td>
<td>1978 (12 days)</td>
<td><em>Clostridium sordelli</em></td>
<td>11</td>
<td>Contaminated thimerosal solution used to disinfect diaphrags of blood culture bottles in laboratory</td>
</tr>
</tbody>
</table>

\(^{1}\)Current nomenclature, *Acinetobacter lwoffi*.

\(^{2}\)Multiple hospitals experienced pseudobacteremias.
have been linked to alcohol solutions contaminated by 
Clostridium spores. Iodine-containing disinfectants have 
only weak sporidial activity, but true infections (or pseudo-
infecteds) stemming from a contaminated solution have, 
to my knowledge, never been reported. Tincture of 
iodine (2%) can be compounded in the hospital's pharmacy
very inexpensively and is rapidly and reliably cidal against
all vegetative bacteria and fungi; commercial iodophors are
almost as effective but are considerably more costly.
Heeding the experience reported by Lynch et al., hospital
laboratories not using an iodine-containing agent for
disinfecting diaphragms of blood culture bottles possibly
ought to consider switching to one, preferably tincture of
iodine.

Epidemics of pseudoinfection have not been confined
solely to bacteremia, but in recent years have also included
pseudoneumonia, pseudotuberculosis, pseudogastroen-
teritis, and particularly, pseudomeningitis, due to nonviable
contaminants in CSF collection tubes or encountered during Gram-staining, both of which resulted in false-positive Gram-stained smears. Stringent quality control measures in clinical laboratories (which should include culturing the penicillinase, if it is even to be used) and active infection control programs have fundamental importance beyond satisfying the requirements of accreditation authorities.

It can be expected that pseudoinfections and pseudoe-
pidemics will continue to occur in the future, but awareness of these phenomena and prompt, meticulous investigations such as the one carried out by Lynch et al. can quickly identify a problem and expedite its resolution.

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