Prevalence of peritonitis-associated coagulase-negative staphylococci on the skin of continuous ambulatory peritoneal dialysis patients

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SUMMARY

The predominance of coagulase-negative staphylococci as normal skin flora is thought to be a factor in their association with episodes of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis. We investigated the prevalence of peritonitis-associated strains on the skin of 28 patients undergoing peritoneal dialysis. Coagulase-negative staphylococci were the most frequently isolated organisms, comprising 47% of peritoneal dialysis fluid isolates and 59% of body site isolates. A total of 142 coagulase-negative staphylococci were speciated, tested for their antimicrobial sensitivity and slime production, and identified by phage typing and plasmid-profile analysis. Staphylococcus epidermidis was the most commonly identified species from both peritoneal dialysis fluid (73%) and body sites (53%). Multiple antibiotic resistance was common, and the greater proportion of isolates were resistant to methicillin: 63.6% of peritoneal dialysis fluid isolates and 61.7% of body-site isolates. S. haemolyticus isolates were significantly more resistant to methicillin than other species. By phage typing and plasmid-profile analysis it was shown that peritonitis was rarely caused by skin-colonizing strains. In only 3 of 14 patients were peritonitis-associated strains isolated as skin colonizers, and no patients developed peritonitis due to organisms previously isolated as skin colonizers.

INTRODUCTION

The predominance of coagulase-negative staphylococci (CNS) as normal skin flora is thought to be a factor in their association with episodes of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) (West et al. 1986; Eisenberg et al. 1987). In recent years, at Royal Prince Alfred Hospital (RPAH), Sydney, there has been an increase of peritonitis in CAPD patients due to methicillin-resistant strains of CNS. To determine if peritonitis-associated strains of CNS were prevalent skin colonizers, we studied isolates from body sites and from peritoneal dialysis fluid (PDF) obtained from CAPD patients on admission to our renal unit.
MATERIALS AND METHODS

Patients

All patients presenting with CAPD associated peritonitis to the Renal Unit, RPAH, from February to November 1987 were included in the survey. Peritonitis was defined as an episode of abdominal pain together with cloudy dialysate and a leucocyte count of > 10^7 cells/l. If a new organism was isolated 1 month after the cessation of antibiotic treatment for a previous peritonitis it was considered as an initial episode. Reinfection was defined as peritonitis caused by the same organism 1 month after cessation of antibiotic treatment.

Culture of bacterial isolates

PDF specimens and swabs from anterior nares, axilla, groin and Tenckhoff catheter sites were taken at each admission to the unit. Dialysate fluid (5 ml) was added to each of two Bactec bottles (Becton Dickinson) in the unit. Heparin (50 µl) was added to the remainder of the dialysate bag which was forwarded with the Bactec bottles to the microbiology laboratory. They were cultured aerobically and anaerobically and examined daily for 6 days. After a Cytur test (Boehringer Mannheim) was performed, the dialysate fluid (20 ml) was centrifuged and the deposit cultured onto blood agar aerobically and anaerobically, MacConkey agar aerobically and cooked meat medium (subcultured at 48 h).

The body-site swabs were cultured onto blood agar and MacConkey agar. Isolates were initially identified by colonial morphology and confirmed by Gram stain and biochemical tests. Slide coagulase-negative staphylococci were further characterized by biochemical reactions, antimicrobial susceptibility, phage typing and plasmid-profile analysis.

Varied colonial morphology of CNS was observed in many swab cultures. Five individual colonies of each colonial type were tested and duplicate isolates were not included in the survey. Isolates were stored in 4% glycerol and 2% skim milk (Difco) at −20 °C.

Speciation

Species determination of CNS was performed by using a combination of two methods:

1. A replica technique, as described by Reuther (1986), based on the Kloos and Schleifer biochemical typing scheme. Five colonies of each isolate were touched by a wire loop and inoculated into 4 ml of peptone water, to give a concentration of approximately 1–5 × 10^7 colony-forming units (c.f.u.)/ml. Aliquots (0.01 ml) were then replicated onto agar plates containing fructose, D-mannose, maltose, lactose, trehalose, mannitol, xylose and sucrose. Each isolate was also tested for DNAase, haemolysin production and novobiocin susceptibility. S. saprophyticus isolates were also tested for lincomycin susceptibility.

2. API 20 Staph kits (API System, Montalieu Vercieu, France) as directed by the manufacturer.

Antimicrobial susceptibility

A replica plate technique was also used to perform sensitivity tests (Washington
Coagulase-negative staphylococcal peritonitis

Aliquots (0.01 ml) of the inoculum (prepared as above to give 1–5 × 10⁶ c.f.u./ml) were replicated onto the antibiotic agar. Antibiotic concentrations were (mg/l): penicillin 0.125, methicillin 4.0, erythromycin 1.0, tetracycline 4.0, chloramphenicol 8.0, fusidic acid 1.0, rifampicin 0.125, vancomycin 4.0, sulphonamide 64.0, trimethoprim 1.0, gentamicin 2.0, novobiocin 2.0, lincomycin 4.0, cephalothin and cefamandole 4.0, 16.0, 128.0 and cefotaxime 4.0 and 8.0. Results were read after 18 h incubation at 37 °C. An additional set of methicillin plates was incubated at 30 °C. Isolates were considered resistant if more than three colonies of visible growth were present. Resistance to cephalothin, cefamandole and cefotaxime were measured at 16.0, 16.0 and 8.0 mg/l respectively.

Slime production

Slime production, in this study, refers to the ability of CNS to coat smooth surfaces with a mucoid layer of bacteria and extracellular material and was assessed by the method of Christensen et al. (1982). Trypticase soy broth (10 ml) in a glass tube was inoculated with a loopful of organisms from a blood agar plate and incubated for 18 h at 37 °C. The culture tubes were then emptied, rinsed with distilled water and stained with safranin. Three independent observers examined each tube and slime production was recorded as positive if a visible film lined the walls of the tube. Ring formation at the liquid–air interface was not considered indicative of slime production. Inter-observer agreement was 99%.

Bacteriophage typing

Phage typing of CNS isolates was carried out by the method described by De Saxe & Xotley (1978). Twenty phages made up the basic set (which was kindly supplied by Dr R. Marples, Colindale, London): RG, 15, 27, 28, 37, 155, 165, 28A, A6C, A9C, 71, 275, 48, 82, 456, 157 A, 471 A, 459, 275 A and B1. One experimental phage, 12, isolated from a clinical S. epidermidis strain from the Royal Prince Alfred Hospital (RPAH) was also used. All phages were used at 100 times the routine test dilution (RTD). Phage typing of S. aureus isolates was carried out by the method described by Blair & Williams (1961).

Plasmid isolation

Plasmid profiles were obtained using a modification of the procedure described by Takahashi & Nagano (1984). Stock cultures of each isolate were plated onto blood agar and incubated overnight at 37 °C. The resultant thick lawn was suspended in 1 ml of 50 mM EDTA, 100 mM NaCl in an Eppendorf tube. The tube was vortexed then spun in a benchtop centrifuge (Hettich, Mikroliter) at 15000 g for 10 s. The supernatant was aspirated and the pellet resuspended in 200 µl of lysostaphin solution (12 units of lysostaphin per ml of 100 mM NaCl, 40 mM-Tris, 50 mM-EDTA pH 6.9). The suspension was mixed by inversion then incubated at 37 °C for 5 min. One hundred microlitres of lysis solution (freshly prepared by adding equal volumes of 0.4 N NaOH and 4% SDS, 100 mM-Tris, 50 mM-EDTA) was added. The tube was inverted 5–10 times and allowed to stand at room temperature for 5 min. For neutralization, 300 µl of cold 3 M sodium acetate pH 5.2 was added and mixed by inversion, maintained at 0 °C for 5 min then centrifuged at room temperature for 2 min. The supernatant was transferred
to another tube and an equal volume of chloroform/isoamyl alcohol mixture (24:1) was added. The solution was emulsified by inversion 5–10 times followed by centrifugation at 4 °C to break the emulsion. The upper aqueous phase was carefully transferred to another tube. One millilitre of ethanol at −20 °C was added to the tube which was maintained at 0 °C for 5 min and then centrifuged at 4 °C for 10 min. The precipitate was dried at room temperature for 5 min and dissolved in 40 μl of TE buffer (100 mM-Tris, 50 mM-EDTA pH 8.0) and stored at −20 °C. A strain of *S. epidermidis*, SK68 (kindly supplied by R. Skurray, Monash University, Victoria) containing pSK101, a tetracycline resistance plasmid of 2.8 Megadaltons (MDa) was included as a control (Tennant, May & Skurray, 1984).

**Agarose gel electrophoresis**

A horizontal maxi-gel composed of agarose (0.7%) (Seakin, FMC, Bioproducts) in electrophoresis buffer (40 mM-Tris-acetate, 10 mM-EDTA) was used. Prepared DNA (20 μl) was mixed with 5 μl of dye solution (60% glycerol, 0.25% bromophenol blue and EDTA 200 mM) and added to the wells of the gel. A marker (1 μl), containing λ phage DNA cut with *Hin dIII* (Pharmacia) and diluted with 19 μl of TE buffer was mixed with 5 μl of dye solution and run with each gel. The gel was submerged in electrophoresis buffer, subjected to electrophoresis at 20 V for 18 h, stained with ethidium bromide and destained. Using a u.v. transilluminator, DNA bands were visualized and photographed with positive/negative film (Polaroid 665).

**Statistical analysis**

Data was analysed by using the χ² test with Yates’s correction of Fisher’s test of exact probability where appropriate.

**RESULTS**

There were 28 patients in the survey and they experienced a total of 47 episodes of peritonitis including four cases of reinfection. Body-site swabs numbering 132 were cultured from the patients’ anterior nares, axilla, groin and Tenckhoff exit sites. The microorganisms isolated from these cultures and the dialysate fluids are shown in Table 1. CNS were the most frequently isolated organisms accounting for 22 (47%) isolates from PDF and 78 (59%) isolates from body sites. Fourteen patients had 22 episodes of CNS peritonitis. *S. aureus* was the second most common isolate, comprising 12.8% of PDF isolates and 15.9% of body-site isolates. Seven (14.9%) isolates from PDFs were Gram-negative organisms. There were nine cases of culture-negative peritonitis and 35 of the body-site cultures yielded no growth. Four cases of reinfection occurred: one CNS, two *S. aureus* and one *Escherichia coli*.

**Species classification**

Biotyping speciated 139 (97.9%) CNS isolates. Of these, 121 were identically speciated by the replica technique and the API 20 system. There was a range of API profiles recorded for each species. In the 18 instances of disparity the API 20 system speciation was accepted. The highest level of agreement was found when
identifying *S. epidermidis, sensu stricto* (96.3%) which was the most frequently isolated species (Table 2). *S. epidermidis* caused 16 (73%) cases of peritonitis and was isolated from 64 (53%) body-site swabs. *S. haemolyticus*, the second most common species was isolated from two (9%) PDF specimens and 27 (22.5%) body-site swabs.

Twelve isolates were not identifiable by the replica technique but were identified as 5 *S. hominis*, 3 *S. simulans* and 4 *S. saprophyticus* isolates by the API 20 system. Two of the *S. simulans* isolates were VP positive. One *S. saprophyticus* isolate, from PDF, was resistant to novobiocin and sensitive to lincomycin and three isolates, from body sites, were sensitive to both antibiotics. Three isolates identified as *S. epidermidis* by the replica technique were reclassified as *S. haemolyticus* by the API 20 system; they were phosphatase, mannos and trehalose negative. One isolate identified as *S. haemolyticus* by the replica technique was reclassified as *S. hominis* by the API 20 system; this isolate was mannitol positive. Two isolates identified as *S. hominis* by the replica technique were identified as *S. haemolyticus* by the API 20 system; they were mannitol negative. Three isolates were not identified by either method. There was no relationship between a particular API 20 profile and other epidemiological markers.
Antimicrobial susceptibility

Multiple antibiotic resistance was common in CNS: 12 PDF isolates (54.5%) and 77 body site isolates (64.2%) showed resistance to five or more antibiotics ($P > 0.05$) (Table 3). Less than 5% were susceptible to all antibiotics. Fourteen (63.6%) PDF isolates and 74 (61.7%) body-site isolates were resistant to methicillin and all showed resistance to four or more antibiotics. Nineteen patients (67.8%) were colonized by methicillin-resistant isolates confirming the widespread distribution of these organisms. Methicillin resistance occurred in all species: $S. \text{haemolyticus}$ isolates (88.9%) were significantly more resistant than $S. \text{epidermidis}$ isolates (57.5%) ($P < 0.05$) and $S. \text{hominis}$ isolates (57.1%) ($P < 0.05$) (Table 4). Resistance to the cephalosporins was found only in methicillin-resistant strains. Nine $S. \text{haemolyticus}$ strains and one $S. \text{epidermidis}$ strain were resistant to all three cephalosporins. Twenty isolates showed resistance to cefotaxime only (10 $S. \text{haemolyticus}$, 6 $S. \text{epidermidis}$ and 4 $S. \text{hominis}$). The remaining methicillin-resistant isolates were sensitive to all three cephalosporins tested.

Individual patterns of antimicrobial susceptibility, although identifying duplicate isolates from the same patient, were too varied to be of epidemiological use.
Coagulase-negative staphylococcal peritonitis

Table 4. Methicillin-resistance of coagulase-negative staphylococcal species

<table>
<thead>
<tr>
<th>Species</th>
<th>Percentage resistant (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PDF†</td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>687 (16)</td>
</tr>
<tr>
<td><em>S. haemolyticus</em></td>
<td>100 (2)</td>
</tr>
<tr>
<td><em>S. hominis</em></td>
<td>0 (1)</td>
</tr>
<tr>
<td><em>S. capitis</em></td>
<td>0 (0)</td>
</tr>
<tr>
<td><em>S. warneri</em></td>
<td>0 (1)</td>
</tr>
<tr>
<td><em>S. saprophyticus</em></td>
<td>100 (1)</td>
</tr>
<tr>
<td><em>S. simulans</em></td>
<td>0 (1)</td>
</tr>
<tr>
<td>Not speciated</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>63.6 (22)</td>
</tr>
</tbody>
</table>

* n. number tested.
† PDF: peritoneal dialysis fluid.

Bacteriophage typing

Only strong reactions (≥ 20 plaques) were recorded. Sixty-two isolates (43.6%) were phage typable. Twenty-two (15.5%) were typed with the Colindale set of phages; 5 isolates from one patient (both body sites and PDF) showed lysis with phage RG and 17 isolates gave a variety of phage-typing pattern reactions. No common phage-typing pattern was identified nor was a particular phage type related to antibiotic resistance. For example, two isolates which gave the following long phage-typing patterns 155/A6C/456/471A/459/B1 and 155/A6C'/456/471 A/459/275 A were resistant to six and three antibiotics respectively; while two isolates with short patterns 48/12 and 48/459 showed resistance to four and eight antibiotics respectively. Forty isolates (29%) typed with our experimental phage 12 only; though this increased the typability rate discrimination between isolates with this phage type was a problem. In 11 patients with CNS peritonitis, phage typing differentiated the PDF isolates from body-site isolates. No phage type was related to any particular plasmid profile.

Slime production

There was no significant difference in the incidence of slime production between PDF isolates (72.7%) and body-site isolates (74.2%) (P > 0.05). Isolates from all species except *S. saprophyticus* produced slime. The proportion of slime-positive isolates among species varied significantly: 87.5% of *S. epidermidis* isolates compared with 66% of *S. haemolyticus* isolates (P < 0.05) and 50% of *S. hominis* isolates (P < 0.05). There was no relationship between slime production and other epidemiological markers.

Plasmid profiles

The plasmid profiles of 22 PDF and 88 body-site isolates were analysed. Eighty-five isolates had 1-14 plasmids which varied in size (some bands presumably represented open forms of DNA). Twelve PDF and 13 body-site isolates were found to contain no plasmids. Linear molecular markers (λDNA) and a lysate of
Fig. 1. Agarose gel electrophoresis of DNA in lysates in SK68, containing the 2.8 MDa plasmid pSK101 and CNS strains isolated in chronological order from PDF (P) and body sites (B) from patient 1. λDNA cleaved with Hinc II; with fragment sizes in kilobases shown on right.

SK68 containing pSK101 (Tennant, May & Skurray, 1984) were run with each gel. We found that pSK101 (covalently closed circular DNA) known to be 2.8 MDa migrated at a rate close to that of the 2.32 kilobase (kb) fragment of λDNA. Only three tetracycline resistant isolates, each from a different patient, showed plasmids migrating at the same rate as pSK101. Etienne et al. (1988) report a prevalent plasmid of 2.8 MDa isolated from S. epidermidis strains all of which were resistant to tetracycline. However, Tennant, May & Skurray (1984) suggest that up to 30% of tetracycline resistant S. epidermidis isolates carry the resistance gene on the chromosome.

Nine gentamicin-resistant isolates, from four patients, contained large plasmids which migrated more slowly than the 2.33 kb fragment of λDNA. Jaffe et al. (1982) report the presence of large plasmids in strains of CNS resistant to gentamicin. Also gentamicin resistance has been found to be encoded on the transposon Tn4001 in staphylococcal species (Lyon, May & Skurray, 1984). Multiple isolates with identical plasmid profiles were isolated from individual patients but isolates from different patients produced markedly different plasmid profiles.
PDF isolates from ten patients had plasmid profiles which clearly differentiated them from body-site isolates. For example, plasmid profiles from one patient (Fig. 1) show sequential PDF isolates and body-site isolates, taken over a period of 7 months. These profiles differed from plasmid profiles of isolates from a second patient (Fig. 2). Again the plasmid profile of the PDF isolate from this patient differs from plasmid profiles of body-site isolates. This differentiation by plasmid-profile analysis was identical, in seven of these patients, to the differentiation obtained by phage typing the isolates. Three isolates were non-typable.

Identification of peritonitis-associated strains: correlation with colonizing strains

In our study separate CNS isolates were considered to be the same strain if speciation by API 20 system, antimicrobial susceptibility, slime production,
phage type and plasmid profile of the isolates were identical. None of these markers alone provided reliable discrimination.

Strain identification showed that of the 14 patients with CXS peritonitis 6 had multiple episodes of CXS peritonitis caused by different strains. There was one episode of reinfection. Two patients had several relapses defined as a recurrence of peritonitis caused by the same organism within one month of cessation of antibiotic treatment, which were followed by new episodes of CXS peritonitis.

Sequential cultures of body sites showed that patients were colonized by the same species of CXS. Strain identification showed that in five cases patients were colonized by particular strains over a period of 1–5 months. Peritonitis was rarely caused by colonizing strains. In only 3 of the 14 patients was the CXS peritonitis-associated strain identical to a colonizing strain. In one case the strain, which was speciated as *S. epidermidis*, and whose plasmid profile is shown in Fig. 3, was phage type 82/A6C, resistant to penicillin, methicillin, tetracycline, sulphonamide and trimethoprim, and was isolated from axilla and PDF on the same day. In the
second case the S. epidermidis strain contained no identifiable plasmids, was phage type 48/82/157 A, sensitive to all antibiotics tested and had been isolated from axilla and PDF on the same day. In the third case previous body-site swabs had not yielded the infecting organism and the S. haemolyticus strain isolated from PDF was isolated later from body sites. This suggested colonization followed infection. No peritonitis-associated strains were isolated from body sites prior to infection in any of the 28 patients. The only organism, other than CNS, isolated from both PDF and body sites was a strain of S. aureus (phage type 29/52 A).

**DISCUSSION**

Studies have demonstrated that coagulase-negative staphylococci are pathogens commonly causing peritonitis in patients undergoing CAPD. Coagulase-negative staphylococci are also ubiquitous skin flora and S. epidermidis the most frequently isolated species. It has been suspected that skin colonization with coagulase-negative staphylococci, followed by access to the peritoneum via catheters is a probable route of infection (West et al. 1986). Strain identification is essential to investigate this possibility. Speciation by biotyping is well documented but as it does not identify strains it has been found to be of limited epidemiological use (Parisi. 1985). In this study, speciation by API 20 system confirmed S. epidermidis as the most common coagulase-negative staphylococcal skin colonizer and causative agent of coagulase-negative staphylococcal peritonitis. We found the replica technique gave good correlation with the API 20 system in identifying S. epidermidis sensu stricto. As S. epidermidis has been reported to be a significant pathogen especially in prosthetic device associated infections such as CSF shunt infections (Younger et al. 1987) the replica method may be a useful cheap diagnostic tool in a routine clinical laboratory for identifying this organism.

As well as S. epidermidis other coagulase-negative staphylococcal species were isolated from both peritonitis and body sites. S. haemolyticus, in this study, accounted for 9% of peritonitis-associated isolates but was more common as a skin colonizer (22-5%), with a widespread distribution. Sixteen patients (73%) were colonized by several different S. haemolyticus strains which were isolated from all body sites predominantly from the groin. A lower prevalence of S. haemolyticus has been reported in some studies (West et al. 1986; Eisenberg et al. 1987) however Deighton et al. (1988) found it to be a common skin colonizer.

This study reports the prevalence of multiple antimicrobial resistant coagulase-negative staphylococci both as skin colonizers and peritonitis-associated organisms. The frequency of methicillin-resistant isolates was higher than reported in other studies (Gill, Selepak & Williams, 1983; Hamilton-Miller & Iliffe, 1985; Baddour et al. 1986). The diversity of species resistant to methicillin and their widespread distribution were interesting observations. However, as strain identification showed there was no common strain among methicillin-resistant coagulase-negative staphylococci the unspecified term ‘MRSE’ encompassed a heterogenous group of organisms. Resistance to the cephalosporins tested was most marked in methicillin-resistant isolates of S. haemolyticus. Some methicillin-resistant strains of S. epidermidis were resistant to ceftoxime but the majority of
strains were susceptible to all three cephalosporins tested. These findings are in accordance with the report of Hamilton-Miller & Iliffe (1985).

Slime production, as measured in this study, was not useful as an epidemiological marker. There was no significant difference in the ability of peritonitis-associated isolates to produce slime compared with colonizing isolates ($P > 0.05$). However other studies have measured the adherence properties of coagulase-negative staphylococci by reading the optical density of a stained adherent bacterial film, and showed a marked difference in adherence between clinical and colonizing strains (Baddour et al. 1986; Younger et al. 1987). As a recent report by Peters et al. (1987) suggested that slime can be determined by reactivity to mannose-specific lectins, slime production, as measured in this study by the tube assay, may be observing ‘adherent’ properties of bacteria.

Strain identification was achieved by the use of plasmid-profile analysis and phage typing either separately or in combination where possible. Parisi et al. (1986) considered plasmid profiles alone or in combination with phage typing the most useful way to type coagulase-negative staphylococcal strains. In our study plasmid profiles were found to be unique to coagulase-negative staphylococcal strains from individual patients, and were able to discriminate between body-site strains and peritonitis-associated strains. Recently, Eisenberg et al. (1987) have reported similar observations.

Phage typing of strains was particularly useful when plasmid profiles could not be obtained and also differentiated body site strains from peritonitis strains. The use of phage 12 isolated locally greatly improved the typability rate and more phages isolated from local strains could improve the discrimination between an even higher percentage of strains. Parisi et al. (1986) for example, typed 91% of coagulase-negative staphylococcal strains using locally isolated phages. Richardson & Marples (1987) reported that CNS isolates showing long-phage-typing patterns were associated with antibiotic susceptibility and that those with short patterns A9C/48, 48 and A9C were related to antibiotic resistance. In this study, however, no relationship between phage type and antibiotic resistance was found as isolates with either long or short patterns were multiply antibiotic resistant and no particular phage type was related to any other epidemiological marker. A lack of correlation of epidemiological markers for coagulase-negative staphylococci was also reported by Mickelsen et al. (1985).

In some studies strain identification of coagulase-negative staphylococci has been used to evaluate the role of skin colonizers in the development of infection (Archer et al. 1984; Eisenberg et al. 1987). Eisenberg et al. (1987) reported that ‘plasmid patterns of coagulase-negative staphylococci demonstrated peritonitis-associated strains usually to be different from isolates cultured from body surfaces’. They also found that there was a rapid turnover of individual strains of coagulase-negative staphylococci on the skin of patients undergoing CAPD. By using a combination of epidemiological markers we were able to show that in most cases peritonitis-associated strains were not found as colonizers of individual patients. As peritonitis-associated strains were not isolated from any body site before infection, the pathogen may have been present in numbers too small to be detected, or may have been exogenously acquired.
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REFERENCES


