Acute Acalculous Cholecystitis

An Increasing Entity

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Acute acalculous cholecystitis was observed to increase in frequency between 1950 and 1979, an increase that was statistically significant. The greatest part of this increase occurred between 1965 and 1979. Acute acalculous cholecystitis was also found to be associated with a higher mortality rate, more than twice that of acute calculous cholecystitis. Acute acalculous cholecystitis occurred in a variety of clinical settings including bacterial sepsis, severe trauma including surgical trauma and burns, multiple transfusions, and severe debilitation. The lesion in the gallbladder consists of intense injury of blood vessels in the muscularis and serosa similar to those induced experimentally by *in vivo* activation of factor XII dependent pathways. Possibly because of the intensity of vascular injury, acute acalculous cholecystitis with minimal clinical manifestations may rapidly progress to gangrene with perforation. Undelayed surgical treatment, which has become more widely accepted over the past 50 years, is essential. It may have also contributed to the increased recognition of this clinical entity.

LINDBERG, GRINNAN, AND SMITH in 1970[1] reported 12 patients who were young Viet Nam casualties and developed acute acalculous cholecystitis during the postoperative period. Various factors were considered to be significant, including the extent of the injury, the magnitude of the operative procedure, the presence of infection, and multiple blood transfusions. There were two deaths, a mortality of 16.6%.

Their report led to a review of patients with acute acalculous cholecystitis treated surgically at the New York Hospital-Cornell Medical Center over a 45-year period (1932–77).[2] One hundred thirty-nine patients were reported. The mortality was 6.5% for the 139, whereas the mortality for 2,114 patients during that same period with acute cholecystitis with calculi was 3.4%. The diagnosis of acute acalculous cholecystitis was confirmed at operation.

Over a two-year period (1977–79), we have treated an additional 13 patients, seven were 65 or older, all were seriously ill. Four died, a mortality of 30.7%. In this same two-year period, two patients who died following extensive burns were also found at postmortem examination to have acute acalculous cholecystitis.

These observations suggested to us that acute acalculous cholecystitis is an entity that is increasing in frequency.

The purpose of this communication is to report the increasing incidence of this entity between 1950 and 1979, to describe the case histories of patients with acute acalculous cholecystitis observed between 1977 and 1979, and to illustrate the histopathologic changes observed in the gallbladder when specimens were available as the result of surgery or postmortem examination.

Methods

Patient Histories

Histories and charts of all patients with a diagnosis of acute cholecystitis between September 1, 1977 and September 1, 1979 were reviewed.

Statistical Analyses

Chi square analysis with Yates' correction factor and chi square analysis of linearity were performed as described by J. L. Fleiss.[3]

Histopathologic Preparations

Blocks of surgically resected gallbladders from patients with acalculous cholecystitis were fixed in 10%

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TABLE 1. *Occurrence of Acalculous and Calculous Cholecystitis*

Years	Acalculous Cholecystitis	Calculous Cholecystitis	Total Acute Cholecystitis	Percent Acalculous Cholecystitis
1932-34	5	89	92	5.4
1935-39	14	195	209	6.7
1940-44	10	195	205	4.9
1945-49	14	170	184	7.6
1950-54	5	165	170	2.9
1955-59	7	212	219	3.1
1960-64	11	216	227	4.8
1965-69	23	322	345	6.7
1970-74	27	343	370	7.3
1975-79	36	344	380	9.5

buffered formalin and ultimately embedded in paraffin prior to sectioning. Blocks of gallbladder and other tissues obtained at autopsy were fixed in Zenker's formalin and also embedded in paraffin. All paraffin sections were stained with hematoxylin. Slides were examined, and photomicrographs made with a Leitz photo microscope.

Results

Results are shown in Tables 1 and 2.

It is shown in Table 1 that acute acalculous cholecystitis (AAC) has steadily increased in frequency between 1950 and 1979. This increase has been linear (slope = .0027) and chi square test of this linear trend reveals it to be statistically significant ($X^2 = 14.18$, $p < 0.001$). This number of patients with AAC among those with a clinical diagnosis of acute cholecystitis is significantly increased from 1965 to 1979. Chi square with Yates' correction factor (Xc^2) = 7.38, $p < 0.01$.

It is shown in Table 2 that the average mortality associated with AAC is 6.9%, while the mortality associated with acute calculous cholecystitis (ACC) is 3.28%. This difference measured between 1932 and 1979 and tested by chi square with Yates' correction factor is significant ($Xc^2 = 10.9312$, $p < 0.005$).

It can also be seen that the mortality of ACC is also increased in the years 1955–1979 over that in the years 1932–1954. This increase is significant, $Xc^2 = 6.058$, $0.05 > p > 0.025$. The mortality associated with AAC has not increased significantly between 1932 and 1979, $Xc^2 = 1.5750$, $.25 > p > 0.100$.

However, even if the mortality associated with AAC (9.6%) and with ACC (4.3%) are compared between the years 1955 and 1979 it can be demonstrated that mortality associated with AAC is significantly greater, $Xc^2 = 7.3664$, $0.01 > p > 0.005$.

Case Reports

Case 1. A 55-year-old male 42 days later developed acute acalculous cholecystitis following a subtotal gastrectomy performed for a duodenal ulcer with perforation. Three transfusions had been given. A cholecystostomy was done. His condition remained precarious. A wound dehiscence occurred four days later. Thereafter, the sepsis gradually subsided, and much improved he was discharged 62 days following the gastric resection.

Case 2. A 59-year-old male, a known diabetic was operated upon as an emergency for a perforated duodenal ulcer of several days. Unsuspected acute acalculous cholecystitis was found, and a cholecystostomy done. The septic course persisted and was uncontrolled by intensive specific and supportive measures. Death occurred in the immediate postoperative period. Autopsy was not performed.

Case 3. An 85-year-old woman with a history of longstanding chronic pulmonary disease, angina, and gastrointestinal bleeding was admitted with acute cholecystitis. She had had transfusions. Twenty-four hours later under general anesthesia an acute acalculous gangrenous gallbladder was removed. Her postoperative course was uneventful, and she was discharged 13 days following admission. Two years later she had a cardiac arrest and resuscitation. She was brought to the emergency room and died five days later.

Case 4. A 79-year-old woman following closure of a ventricular defect was reoperated upon within 24 hours for bleeding. She had received transfusions. She developed septicemia, and on the 17th postoperative day a tracheostomy was done because of increasing debility. Eight days later under local anesthesia an acute acalculous cholecystitis was treated by cholecystostomy. The septicemia continued, and she died 19 days later, 41 days after the repair of the ventricular septal defect. No postmortem examination was obtained.

TABLE 2. *Mortality Associated with Acute Acalculous Cholecystitis (AAC) and Acute Calculous Cholecystitis (ACC)*

	AAC			ACC		
Years	Cases	Deaths	Mortality (%)	Cases	Deaths	Mortality (%)
1932-34	5	1	20	87	3	3.4
1935-39	14	1	7	195	5	2.5
1940-44	10	0	0	195	3	1.5
1945-49	14	1	7	170	4	2.0
1950-54	5	0	0	165	3	1.8
1955-59	7	0	0	212	10	4.7
1960-64	11	0	0	216	9	4.2
1965-69	23	4	17	322	11	3.4
1970-74	27	2	7	343	13	3.8
1975-79	36	4	11	344	19	5.5
Total	152	13	Av. 6.9	2249	80	Av. 3.28

Case 5. A vigorous, 41-year-old woman, mother of three children, with a history of episodes of right upper quadrant pain was admitted with a diagnosis of acute cholecystitis and presumed but not demonstrated cholelithiasis. At operation an acutely inflammed gallbladder with an intra-gallbladder polyp and no stones were removed. Her recovery was uneventful. Microscopic section of the gallbladder was that of acute cholecystitis superimposed on chronic cholecystitis.

Case 6. An 87-year-old male with multiple fractures of the pelvis and lower extremities and soft tissue injuries requiring several surgical procedures and transfusions, was transferred three weeks later to New York Hospital with acute cholecystitis. After 24 hours of preoperative preparation, a cholecystectomy for acute acalculous gangrenous cholecystitis was done. He was discharged 18 days later.

Case 7. A 74-year-old man following a transurethral resection that revealed a carcinoma of the bladder then had a radical cystectomy with the creation of an ileal conduit. He received several transfusions. Thirty days later he was operated upon for acute cholecystitis. Acute acalculous cholecystitis was treated by cholecystostomy. The postoperative course was tedious because of general debility. He was discharged 66 days after the operation for radical cystectomy for carcinoma.

Case 8. A 74-year-old woman markedly debilitated with rheumatoid arthritis, hypertension, and recurrent bleeding from the upper gastrointestinal tract treated by multiple transfusions, was transferred from another hospital with a diagnosis of acute cholecystitis. At operation a cholecystectomy was done for an acalculous gangrenous cholecystitis. One month later she was discharged to the hospital from whence she came in a state comparable to that prior to the onset of acute cholecystitis.

Case 9. An 81-year-old male, a known diabetic with a long history of congestive cardiac failure and arrhythmias with a massive pleural effusion, was admitted for acute cholecystitis. At operation an acute acalculous gangrenous gallbladder with a small perforation was found. A cholecystostomy was done. The immediate postoperative course was one of severe sepsis, which gradually subsided. He was discharged 46 days after operation. He was readmitted three months later, and an elective cholecystectomy done. The common duct was explored. No calculi were present. The postoperative course was uneventful, and he was discharged 12 days after operation.

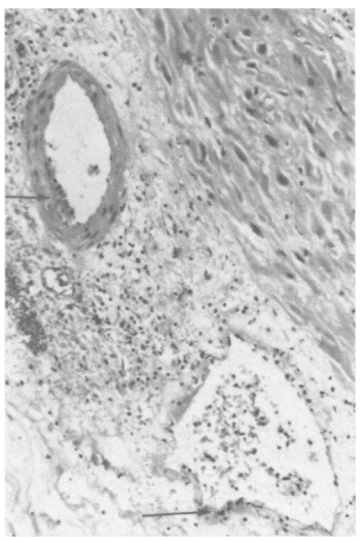

FIG. 1. Artery (upper left) and vein (lower right) in the serosa of the gallbladder removed surgically from patient 10. Hemorrhage infiltrates the subendothelium of the artery (arrow). The wall of the vein is focally necrotic and infiltrated with polymorphonuclear neutrophils (arrow) as is the serosal connective tissue (hematoxylin-eosin ×156).

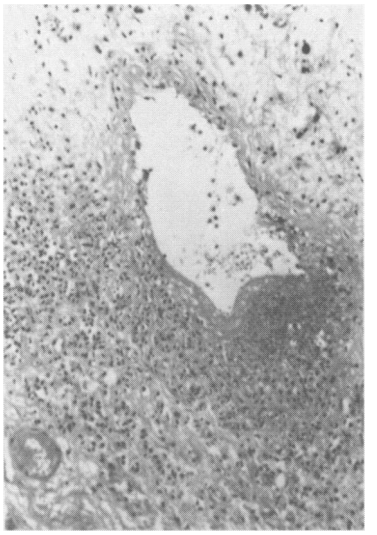

FIG. 2. The wall of a vein in the same gallbladder (Fig. 1) is focally necrotic and extensively infiltrated by acute inflammatory cells (hematoxylin-eosin ×156).

Case 10. A 58-year-old man was transferred from another hospital because of subarachnoid hemorrhage. He had undergone multiple surgical procedures for aneurysms previously and had received numerous transfusions. He was markedly debilitated. Thirty days after admission to New York Hospital he developed an acute abdomen. Cholecystectomy was performed, revealing acute, acalculous cholecystites. He continued to run a septic course but slowly improved with intensive antibiotic therapy and was discharged 30 days after cholecystectomy (Figs. 1–3).

Case 11. A 52-year-old male, with a history of ulcer and considerable debility who had recently been treated with cemetidine, was admitted because of jaundice (bilirubin 4.4). He was afebrile but had a leucocytosis of 14,000. Sonography suggested an enlarged gallblad-

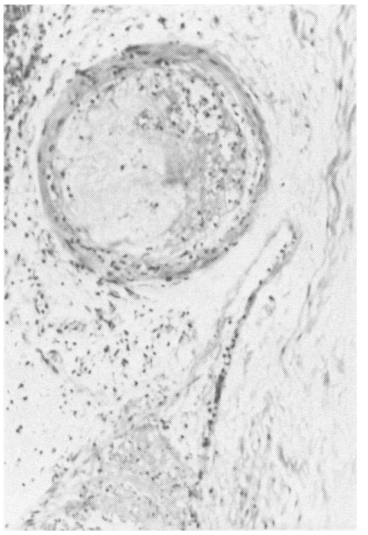

FIG. 3. An artery in the wall of the same gallbladder (Figs. 1, 2) is occluded by thrombus. The wall of a vein is infiltrated with acute inflammatory cells (hematoxylin-eosin ×156).

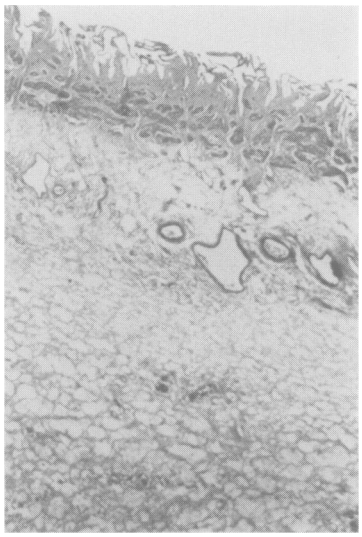

FIG. 4. Lower power view of gallbladder of patient 14. The serosa is markedly edematous (hematoxylin-eosin ×32).

der with a much thickened wall, 0.3 cm, without evidence of common duct obstruction. At operation an acute acalculous cholecystitis was treated by cholecystectomy. An operative cholangiogram was negative for calculi. The postoperative course was uneventful, and he was discharged symptom free 12 days later.

Case 12. A 59-year-old male was transferred from another hospital following resection of an aortic aneurysm for dialysis because of renal failure. He had received many transfusions. While under intensive care, his abdomen became distended with dehiscence of the abdominal wound. At operation for closure of the dehiscence, acute acalculous cholecystitis was found, and a cholecystostomy done. Twenty-five days following the resection of the aortic aneurysm the patient died from renal and hepatic failure with persistent sepsis.

Case 13. A 65-year-old male was admitted with a 50% second and third degree body burn. Intensive treatment was followed by areas of debridement and skin grafting. Sepsis persisted and increased with other complications. He received transfusions. Seventeen days after injury a tracheostomy was done, and a tentative diagnosis of acute cholecystitis was made. At operation acute acalculous cholecystitis was treated by cholecystostomy. Temporary improvement was followed by a gram-negative septicemia, and death occurred 34 days after admission and 17 days postcholecystostomy. No postmortem examination was done.

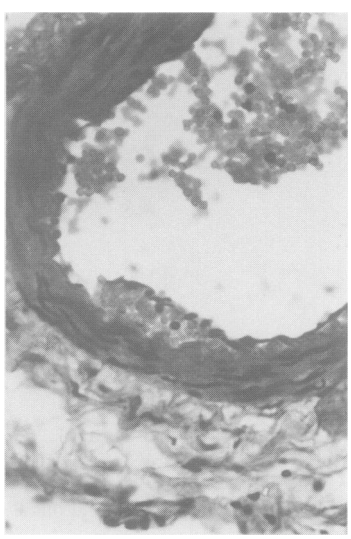

FIG. 5. The endothelium of an artery in the same specimen is dissected from the underlying muscularis (hematoxylin-eosin ×500).

Two patients in whom an acute acalculous cholecystitis was revealed at autopsy unsuspected.

Case 14. A 4-year-old girl sustained second and third degree burns over one-third of body surface, with severe smoke inhalation. Severe sepsis, pneumonitis, and tracheitis were uncontrolled. Death occurred 14 days following burn. Postmortem examination revealed an acute acalculous cholecystitis. The gallbladder was enlarged and edematous. Death was caused by severe pulmonary edema and pneumonia (Figs. 4–6).

Case 15. A 58-year-old male sustained second and third degree burns over one-third of the body surface, including face and upper one-half of the body. Severe shock was controlled, but sepsis, pulmonary edema, and bronchopneumonia were persistent over the ensuing 13 days.

At postmortem examination the gallbladder wall was grossly edematous without evident obstruction of the cystic duct or common bile duct.

Observations

The following summarizes pertinent data concerning the 15 cases reported in this study (1977–79).

1. Eleven (73.3%) had had several blood transfusions or had been on the corporeal mechanism for cardiovascular surgery.
2. Eleven (73.3%) who developed acute acalculous cholecystitis in various clinical settings had severe infections with a variety of gram-negative microorganisms including *Escherichia coli, Klebsiella,* and *Pseudomonas.*
3. Ten (66.6%) had undergone extensive surgery or had had large surface burns.
4. Six (40%) had gangrenous gallbladders.
5. Ten (66.6%) were males.
6. There were six deaths, a mortality of 40%. Three followed extensive surgery and three had suffered large body surface burns.

Histologic Observations

In the sections of gallbladder from the patients who underwent cholecystectomy for acute acalculous cholecystitis and from the two patients who died of complications from burns and who were observed to have acute acalculous cholecystitis at autopsy, the serosa and muscularis of the gallbladder were markedly edematous and in some instances focally necrotic. Focal necrosis of the walls of arteries and veins was present, sometimes associated with thrombosis. The walls of these vessels were infiltrated with polymorphonuclear neutrophils. The serosa and muscularis of the gallbladder were also infiltrated by these cells (Figs. 1–6).

In the two cases illustrated, early changes in blood vessels were observed. These changes consisted of focal injury of the endothelium or intima leading to dissection

of the endothelium by erythrocytes and ultimately thrombosis.

Except in the gangrenous regions in certain gallbladders, the mucosa was relatively uninvolved, and changes were observed predominantly in the muscularis and serosa.

Discussion

The patients described in this report suffered from acalculous cholecystitis, a clinical entity that appears to be increasing in incidence. With one exception all had considerable debility. The nature and extent of the debility may be attributed to one or more coexistent conditions. Major surgical procedures or other trauma, including burns with associated complications are the most frequent preceding conditions.[4,5] Infection, chronic disease such as diabetes, arthritis and rheumatism, and cancer were also commonly associated.

The question arises as to the nature of common mechanisms underlying the development of acute, acalculous cholecystitis. Histologically, the common feature in these cases consisted of intense injury of blood vessels in the muscularis and serosa of the gallbladder.

Such lesions can be produced in dogs[6-8] and monkeys consequent to activation of factor XII Hageman factor dependent pathways by intravenous injection or inhalation of polyphenol or polyphenol containing activators of these pathways or by injection of bacterial endotoxins.

It is known that exposure of plasma to collagen can activate factor XII.[9] It is also known that endotoxin of gram-negative bacteria can activate factor XII.[10] Infusion of albumin preparation containing factor XII fragments resulted in bradykinin hypotension in some patients.[11] Storage of plasma at 4 C can result in the conversion of prekallikrein to kallikrein.[12] Also, material resembling factor XII with prekallikrein activating activity has been found in guinea pig skin.[13] If human skin also contains this material, the possibility is raised that it might be released and activated consequent to major trauma such as burns. Finally many malignant cells synthesize plasminogen activator, release of which into the circulation could result indirectly in activation of factor XII.[14]

Thus trauma, bacterial sepsis, transfusion of blood or blood products, and cancer, which are common preexisting conditions in patients who developed acute acalculous cholecystitis, are all conditions in which activation of factor XII might occur and it is reasonable to hypothesize that this may have occurred in all but one of the patients described above.

In the series of patients presented here the occurrence of acute acalculous cholecystitis in an otherwise healthy, 41-year-old woman remains an enigma, and is not easily explained by this hypothesis. She was not taking birth control pills, which are known to elevate levels of factor XII and decrease levels of Cl 1NH and activity of anti thrombin III.[15,16] She was not a cigarette smoker.[17] Although there is no verbal history in this patient of recent abortion or endometritis that might have resulted in activation of factor XII dependent pathways, the possibility that either of these may have occurred cannot be excluded.

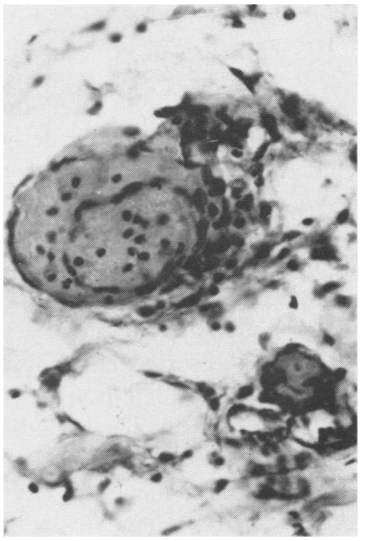

FIG. 6. The endothelium of a small artery has been dissected from the underlying vessel wall. The original lumen and the pseudo lumen are occluded by thrombus. The wall of the vessel (lower right) is also infiltrated by acute inflammatory cells. (hematoxylin-eosin ×500).

In experiments cited above, intravenous injection or inhalation of polyphenol or polyphenol containing substances resulted in activation of factor XII dependent pathways and inflammation in vessels of the gallbladder and to a lesser extent the lung in both dogs and African Green monkeys. Blood vessels in other organs, including the duodenum and pancreas, were spared. Why the gallbladder and lung appear to be a target organ for injury consequent to activation of factor XII dependent pathways is unknown. One may reason, inasmuch as the gallbladder embryologically is derived from the duodenum, which in its maturity and normal state of physiological function is known to contain within its wall cholecystokinin, that a kininogen may exist within the wall of the gallbladder or its vessels. This may be cleaved by active components of the intrinsic pathway to yield vasoactive material capable of augmenting local vasospasm and injury.

The pathogenesis of acute acalculous cholecystitis may be viewed as being different from that of acute calculous cholecystitis. In those with calculous formation obstructing the egress of bile from the gallbladder, there is stasis of bile often with infection. There is also edema of the tissue of cystic duct and at its junction

with the common duct that may interfere with the arterial supply. The calculi may have been within the gallbladder for variable periods of time, and these may have traumatized the mucosa with infection of the gallbladder wall. Such episodes may subside or result in a wide range of changes from edema to necrosis of the gallbladder.

In acalculous cholecystitis, the changes within the blood vessels in the gallbladder are initiated as the chain of events set in motion by activation of factor XII dependent pathways. Injuries to the blood vessels may be followed by edema of the serosa and muscularis, ischemia, and necrosis of a part or all of the gallbladder.

If the conditions described above that can lead to factor XII activation are present in a patient with gallstones, the wall of a gallbladder with calculi may become inflamed, the calculi being incidental. It is reasonable to consider that elderly individuals with cholelithiasis who are debilitated and sustain severe trauma, infection, and impaired physiological function of organ or system may develop cholecystitis, even though the gallstones may never before have caused symptoms, and rapidly destroy integrity of the gallbladder wall. We have in recent years had an increasing proportion of patients admitted for acute cholecystitis in the older age group, 65 and over. These patients have a much higher morbidity and mortality than those who are younger.

From 1950 to 1979 the incidence of acute acalculous cholecystitis has increased linearly. This increase became statistically significant between 1965–1979, when the incidence of acute acalculous cholecystitis among patients with acute cholecystitis was 7.8%, rising to 9.5% between 1975–1979. Between 1932 and 1964 it was 5%. The causes of this increase in incidence are unknown. It can be hypothesized that it is related to increasing age of patients, more extensive and invasive therapeutic procedures, including surgical procedures, and prolonged survival of gravely ill patients increasing the chances of initiation of the disease.

Summary

In the study presented here, the incidence of acute acalculous cholecystitis among patients with acute cholecystitis was observed to have increased significantly beginning in 1950. This increase became increasingly significant from 1965–1979, the period of the study. Acute acalculous cholecystitis was also observed to be associated with more than twice the mortality rate of acute calculous cholecystitis, a result also demonstrated to be statistically significant.

The reported increase in the incidence of acute acalculous cholecystitis in recent years is suggested as being related to the prolonged survival of gravely ill patients, increasing the chances of initiation of the disease and perhaps allowing it to become more severe.

Acute acalculous cholecystitis was revealed by histologic studies of the gallbladder removed from six patients who had cholecystectomy and at postmortem examination of the two patients who died following severe body burns and had not been operated upon. The most significant changes on microscopic examination was focal necrosis of the wall of the arteries and veins of the serosa and muscularis leading to dissection of the endothelium by erythrocytes and ultimate thrombosis in both arteries and veins. These intense injuries to the blood vessels in the serosa and muscularis with sparing of the mucosa are similar to those induced by the authors in dogs and monkeys by the intravenous injection or inhalation of polyphenol or polyphenol containing activators of factor XII on Hageman pathways and also by injection of *E. coli* lipopolysaccharide.

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