MAJOR ARTICLE

Recent Trend of Necrotizing Fasciitis in Taiwan: Focus on Monomicrobial *Klebsiella pneumoniae* Necrotizing Fasciitis

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(See the Editorial Commentary by Lee, on pages 940–2.)

Background. Necrotizing fasciitis (NF) is a rapidly progressive, life-threatening soft-tissue infection that is traditionally caused by group A *Streptococcus* (GAS) or mixed aerobic/anaerobic bacteria. Monomicrobial *Klebsiella pneumoniae* NF (KP-NF) has been reported since 1996 but has not yet been systematically studied.

Methods. We retrospectively studied consecutive NF cases treated at a university hospital in Taiwan during 1997–2010 and investigated the clinical characteristics and outcomes associated with monomicrobial KP-NF, using monomicrobial GAS-NF as a reference. We also analyzed the virulence gene profiles of the isolated *K. pneumoniae* strains.

Results. Of 134 NF cases, 88 were monomicrobial, of which the most common pathogens were GAS (n = 16) and *K. pneumoniae* (n = 15). Monomicrobial KP-NF entailed a moderate risk of limb loss (20% vs 25%; $P = 1.000$) and high mortality (47% vs 19%; $P = .135$), and it was more likely to involve bacteremia (80% vs 31%; $P = .011$), concomitant distant abscesses (27% vs 0%; $P = .043$), and underlying immunocompromising conditions (100% vs 63%; $P = .018$), compared with GAS-NF. The isolated *K. pneumoniae* strains (n = 10) were of capsular polysaccharides genotype K1 (n = 4), K54/K20/K5 (n = 4), K2 (n = 1), and K16 (n = 1). All strains carried *rmpA*, *iucABCDiutA*, and *iroA*. Genotype K1 strains had a significantly higher risk of concomitant distant abscesses, compared with non-K1 strains (75% vs 0%; $P = .033$).

Conclusions. *K. pneumoniae* has become a common pathogen of monomicrobial NF in Taiwan. Physicians treating patients with monomicrobial KP-NF should be aware of the risk of concomitant distant abscesses, particularly in cases caused by genotype K1.

Necrotizing fasciitis (NF), described by Meleney in 1924 as "hemolytic streptococcal gangrene," is a rapidly progressive and life-threatening soft-tissue infection that is characterized by its spread along the fascial planes, resulting in adjacent tissue necrosis and secondary gangrene [1]. Early diagnosis with prompt surgical intervention is crucial in minimizing the associated morbidities and mortality [2].

There are 2 distinct types of necrotizing fasciitis [3]. Type 1 is a polymicrobial infection involving mixed aerobic/anaerobic bacteria [3]. Type 2 is a monomicrobial infection, of which *Streptococcus pyogenes* (group A *Streptococcus* [GAS]) is the most classic pathogen [2, 3]. *Klebsiella pneumoniae* has been documented as one of the bacteria isolated from polymicrobial NF [3, 4] but was traditionally not considered a pathogen capable of causing monomicrobial NF.

Since 1996, however, cases of monomicrobial *K. pneumoniae* NF (KP-NF) have been reported in

Received 7 December 2011; accepted 11 May 2012; electronically published 19 June 2012.

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Clinical Infectious Diseases 2012;55(7):930–9

DOI: 10.1093/cid/cis565

Taiwan [5–7], Hong Kong [8, 9], Singapore [10], Japan [11], and regions outside Asia (eg, Europe [12, 13], Canada [14], and the United States [15–17]). These cases typically occurred in patients with underlying immunocompromising conditions, such as diabetes mellitus or liver cirrhosis [5–15, 17]. Some cases were noted to have concomitant distant abscess(es), including endogenous endophthalmitis [5, 7] and abscess in the liver [5–7, 10, 14], kidney [7, 10], or lung [16]. Deaths have been reported. Capsular serotyping of the *K. pneumoniae* isolates was conducted in merely 3 cases, with 2 showing K1 [7, 15] and the other showing K2 [12]. Only one case was evaluated for other virulence genes, in which the isolate carried *rmpA* and aerobactin [12].

So far, research on monomicrobial KP-NF has been extremely limited. The literature is essentially based on case reports, in addition to a few studies on NF in general that have reported the percentage of KP-NF cases in their samples [18–23]. A systematic study on the clinical manifestations and outcomes of monomicrobial KP-NF is lacking. The risk and determinants of concomitant distant abscesses, as well as the mortality risk, remain unclear. Data on its microbiological characteristics are also scarce. The role of bacterial capsular genotype has not yet been studied either.

This study intended to examine the recent pattern of NF, with a focus on monomicrobial KP-NF. We aimed to systematically investigate the clinical features and outcomes of monomicrobial KP-NF, using the monomicrobial NF caused by GAS as reference. We also analyzed the virulence gene profiles of isolated *K. pneumoniae* strains, including the capsular polysaccharides (*cps*) genotypes [24–26], *rmpA* [24, 26], and the iron-uptake systems [27–29]. Our previous study has shown important differences between *K. pneumoniae* strains of the K1 and the non-K1 genotypes [26]. Genotype K1 strains are significantly more virulent than non-K1 strains, in terms of higher in vitro serum resistance and greater risk of septic ocular or central nervous system complications from pyogenic liver abscesses [26]. Hence, the present study also explored the differences between the K1 and the non-K1 genotypes in monomicrobial KP-NF.

METHODS

Study Setting

The National Taiwan University Hospital (Taipei, Taiwan) is a university-affiliated medical center with a 2200-bed capacity. It provides both primary and tertiary referral care in northern Taiwan. The study procedures were reviewed and approved by the institutional review board.

Identification of NF Cases

We identified all consecutive cases of NF confirmed by surgery between January 1997 and August 2010, using a computerized registry of the patients treated by the Division of Plastic Surgery. The diagnosis of NF was confirmed by independent review carried out by 2 investigators on the basis of intra-operative and histopathological findings, which were characterized by a lack of resistance to blunt dissection of the normally adherent fascia, along with the presence of necrotic fascia and purulent malodorous discharge. Data on the causal microorganisms were determined by reviewing the microbiological reports of wound and/or blood culture samples that were taken before or at the time of operation.

Clinical Data

For the monomicrobial NF cases caused by *K. pneumoniae* and GAS, we used a computerized data collection form to systematically collect the following information from the patients' medical records:

1. clinical manifestations, including the site(s) of NF, local findings on admission, severity of sepsis syndrome, presence of bacteremia, and the existence of concomitant distant abscesses (defined as any abscess lying noncontiguous to the NF sites);
2. preceding local factors, including sharp or blunt injury, skin ulcer, and any other identified local factors or events that occurred over the site(s) of NF prior to its onset;
3. underlying immunocompromising conditions, including malignancy, liver cirrhosis, nephrotic syndrome, alcoholism, use of steroids/immunosuppressives, and diabetes mellitus [26]; and
4. treatments and outcomes, including antimicrobial therapy, surgical interventions, limb loss, and infection-related mortality [26].

K. pneumoniae Strains

Bacterial isolates were cultured, identified, and tested for susceptibility according to standard microbiological methods as previously described [26]. We collected the clinical *K. pneumoniae* strains from blood culture isolates obtained from hospitalized patients and stored them at −80°C until use. We first reviewed the medical records of the monomicrobial KP-NF cases to determine the date on which NF was initially diagnosed and then retrospectively identified the stored *K. pneumoniae* strains for analysis. Colony mucoviscosity was assayed as previously described [24, 26].

cps Genotyping

We conducted *cps* genotyping of K serotype–specific alleles at the *wzy* locus by polymerase chain reaction (PCR) as previously described [26]. The serotype K1 *wzy* allele, *wzy*_K1 (designated as *magA* before 2007; GenBank accession nos. AB085741 and AB355924) [24–26, 30, 31], is essential for the K1 capsular serotype, colony hypermucoviscosity, and high virulence of the prototype tissue-invasive strain *K. pneumoniae* NTUH-K2044 [24–26]. The serotype-specific *wzy* alleles

Table 1. Bacteria Cultured From 134 Necrotizing Fasciitis Cases

NF Type, Causative Pathogen(s)	No. (%)
Monomicrobial	
Streptococcus pyogenes	16 (12)
Klebsiella pneumoniae	15 (11)
Staphylococcus aureus	
MRSA	11 (8)
MSSA	8 (6)
Vibrio vulnificus	9 (7)
Escherichia coli	6 (4)
Aeromonas hydrophila	5 (4)
Others[a]	18 (13)
Polymicrobial	
Mixed aerobic/anaerobic[b]	20 (15)
Others[c]	13 (10)
Culture negative	
Not available[d]	13 (14)
Total	134 (100)

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NF, necrotizing fasciitis.

[a] *Pseudomonas aeruginosa* (n = 3), group B *Streptococcus* (n = 2), group G *Streptococcus* (n = 2), *Streptococcus constellatus* (n = 1), viridans group streptococci (n = 1), *Streptococcus* species (n = 1), *Enterococcus* species (n = 1), *Clostridium septicum* (n = 1), *Serratia marcescens* (n = 1), *Enterobacter cloacae* (n = 1), *Proteus mirabilis* (n = 1), *Aeromonas caviae* (n = 1), non-O1 *Vibrio cholerae* (n = 1), and *Acinetobacter baumannii* (n = 1).

[b] *Veillonella* species and gram-positive bacilli (n = 1); *E. coli* and *Bacteroides gracilis* (n = 1); *Clostridium* species, *Enterococcus species*, and *Candida albicans* (n = 1); MSSA, group B *Streptococcus*, *Peptostreptococcus* species, and *Citrobacter freundii* (n = 1); *E. coli*, *Enterobacter aerogenes*, *Salmonella* O4, *Bacteroides fragilis*, and *Fusobacterium varium* (n = 1); *K. pneumoniae*, viridans group streptococci, *Peptostreptococcus* species, and *Veillonella* species (n = 1); MSSA, *Prevotella* species, *Bacteroides ureolyticus*, and *B. fragilis* (n = 1); *Corynebacterium* species, *Enterococcus* species, viridans group streptococci, and *B. fragilis* (n = 1); *E. coli*, *K. pneumoniae*, *Enterococcus* species, *Bacteroides vulgatus*, *Bacteroides thetaiotaomicron*, and *B. fragilis* (n = 1); group B *Streptococcus*, *Peptostreptococcus anaerobius*, *Prevotella* species, and *Propionibacterium* species (n = 1); *Enterococcus avium*, *B. thetaiotaomicron*, *Bifidobacterium* species, *E. coli*, and *P. aeruginosa* (n = 1); Beta-*Streptococcus* non-group ABD, *Propionibacterium* species, and group F *Streptococcus* (n = 1); *Proteus vulgaris*, *Providencia stuartii*, *B. fragilis*, *Peptostreptococcus* species, and *Prevotella* species (n = 1); *P. mirabilis*, *Citrobacter koseri*, *K. pneumoniae*, *Peptostreptococcus* species, and *B. fragilis* (n = 1); *K. pneumoniae* (extended-spectrum β-lactamase producing) and *B. fragilis* (n = 1); *Enterococcus* species, *C. koseri*, *P. vulgaris*, and *B. fragilis* (n = 1); group G *Streptococcus*, MSSA, *A. baumannii*, *E. cloacae*, *A. caviae*, *Stenotrophomonas maltophilia*, *Klebsiella oxytoca*, *Peptostreptococcus* species, and viridans group streptococci (n = 1); *E. coli* and *B. fragilis* (n = 1); *E. coli* and *Lactobacillus* species (n = 1); and *Aeromonas hydrophila*, *E. coli*, *P. vulgaris*, *Enterobacter* species, and *B. fragilis* (n = 1).

[c] *E. coli*, *P. aeruginosa*, and coagulase-negative staphylococci (n = 1); viridans group streptococci and *Eikenella corrodens* (n = 1); *P. aeruginosa*, *A. baumannii*, *Proteus mirabilis*, and coagulase-negative staphylococci (n = 1); *Enterobacter clocae*, *K. pneumoniae*, *Enterococcus* species, and *C. freundii* (n = 1); *Pantoea agglomerans* and group B *Streptococcus* (n = 1); *Staphylococcus epidermidis* and *C. albicans* (n = 1); coagulase-negative staphylococci, *P. aeruginosa*, *E. coli*, *Enterococcus* species, and *Candida glabrata* (n = 1); group A *Streptococcus* and *C. albicans* (n = 1); group B *Streptococcus* and *Enterococcus* species (n = 1); *E. coli*, *K. pneumoniae*, and *P. aeruginosa* (n = 1); group B *Streptococcus*, *E. aerogenes*, and viridans group streptococci (n = 1); *E. coli* and *Enterococcus* species (n = 1); and *K. oxytoca* and *K. pneumoniae* (n = 1).

[d] Intravenous antimicrobial therapy had been started before or on initiation of the operation, and the wound culture that was taken later during the surgery did not grow organisms.

for capsular serotypes K2, K5, K20, K54, K16, and K57 also exist in corresponding *cps* gene clusters (GenBank accession nos. AB362367, AB289645–AB289650, AB614371, and AB289652) [26, 30]. Supplementary Table 1 lists the PCR primers.

Detection of *rmpA*

The *rmpA* gene, a regulator of exopolysaccharides synthesis, is also required for full virulence of NTUH-K2044 [24]. The genome of NTUH-K2044 (http://genome.nhri.org.tw/KP/) [32] carries 3 different copies of *rmpA* (GenBank accession nos. AB289642–AB289644): 2 (open reading frames [ORFs] KPP020 and KPP302) are on the 224-kb large plasmid pK2044, and the other (ORF KP3619) is on the chromosome [24, 26]. The presence of *rmpA* was determined by PCR as previously described [26]. We first identified the consensus sequence, using common primers, and then verified each different copy by use of specific primers (Supplementary Table 1).

Detection of Iron-Uptake Systems

There are 4 iron-uptake systems: *kfu*, *Yersinia* high-pathogenicity island (HPI; for yersiniabactin production), *iucABCDiutA* (for aerobactin production), and *iroA* [27–29]. They are also needed for full virulence of NTUH-K2044 [27–29]. Both *kfu* and *Yersinia* HPI are encoded on the bacterial chromosome, whereas *iucABCDiutA* and *iroA* are encoded on the large plasmid pK2044 [27–29]. The presence of the 4 iron-uptake systems was determined by PCR, using primers listed in Supplementary Table 1.

Statistical Analysis

All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). Between-group differences for categorical and continuous data were compared using Fisher exact tests and Wilcoxon rank sum tests, respectively. All tests were 2-tailed, with $P < .05$ considered statistically significant.

RESULTS

Bacteria Cultured From NF

We identified a total of 134 NF cases, of which 88 (66%) were monomicrobial, 33 were polymicrobial, and 13 were culture negative (Table 1). The most common pathogens of monomicrobial NF were GAS (n = 16) and *K. pneumoniae* (n = 15). Monomicrobial KP-NF accounted for 17% of the monomicrobial NF cases and 11% of all NF cases.

Clinical Features of Monomicrobial *K. pneumoniae* NF

Table 2 lists the 15 cases of monomicrobial KP-NF. The most frequently involved site was the lower extremities. Many cases had distinctive local signs of either crepitation (20%) or bullous lesions (27%). Bacteremia was common (80%). A total

of 27% of cases (4 of 15) had concomitant distant abscess(es) involving the brain, liver, lung, kidney, and/or intra-abdomen (2 patients had abscess at ≥2 sites). Eight cases (53%) did not have any preceding local injury. All patients had underlying immunocompromising condition(s), of which diabetes mellitus was the most common (100%). Six patients (40%) also had other immunocompromising conditions (Table 2).

Disk Susceptibility and Antimicrobial Therapy

The *K. pneumoniae* isolates in the 14 community-acquired cases were universally susceptible to cephalosporins (cefazolin, cefoxitin, and cefotaxime), aminoglycosides (gentamicin and amikacin), and imipenem, and most (93% [13 of 14]) were susceptible to ciprofloxacin; all were treated with a third- or fourth-generation cephalosporin or a carbapenem (Table 2). The isolate in the hospital-acquired case (from patient 1) was resistant to cefazolin, cefotaxime, gentamicin, and amikacin and was treated with ticarcillin/clavulanate plus tobramycin.

Surgical Interventions, Limb Loss, and Mortality

All 15 patients underwent surgical interventions (Table 2). Three patients (20%) underwent amputation, with each losing 1 limb (below the knee for 2 patients and above the knee for 1). A total of 47% (7 of 15) eventually died from septic shock, including 2 of the 3 patients who underwent amputation.

Comparison With GAS-NF

Compared with GAS-NF cases, monomicrobial KP-NF cases had a similarly moderate risk of limb loss (20% vs 25%) and higher mortality (47% vs 19%; statistically nonsignificant; Table 3). They were more likely to have bacteremia (80% vs 31%; $P = .011$) and concomitant distant abscesses (27% vs 0%; $P = .043$). They were also more likely to have underlying immunocompromising conditions (100% vs 63%; $P = .018$), in terms of diabetes mellitus (100% vs 50%; $P = .002$), and other immunocompromising conditions (40% vs 25%; statistically nonsignificant), as well as a greater number of immunocompromising conditions (mean [± SE], 1.5 ± 0.2 vs 0.8 ± 0.2; $P = .006$, by the Wilcoxon rank sum test).

K. pneumoniae Strains

Blood culture isolates were available for bacterial genotyping in 10 (67%) of the monomicrobial KP-NF cases. Samples were not available in the other 5 cases (Table 4), mainly because of negative results of blood culture, which occurred more frequently in this group than in the former group (3 of 5 vs 0 of 10; $P = .022$). Apart from this, no significant differences existed between those who did and those who did not have samples available for genotyping.

Genotyping of *K. pneumoniae* Strains

K1 was the most common *cps* genotype (n = 4; 40%), followed by K54 (n = 2), K20 (n = 1), K5 (n = 1), K2 (n = 1), and K16 (n = 1; Table 4). All strains carried the 2 plasmid-encoded copies (ORFs KPP020 and KPP302) of *rmpA*, as well as the plasmid-encoded gene clusters *iucABCDiutA* and *iroA*. The chromosome-encoded iron-uptake systems were present in all K1 genotype strains but were less common in non-K1 strains (*kfu*: 100% vs 50%; *Yersinia* HPI: 100% vs 84%; both statistically nonsignificant).

K1 Versus Non-K1 Genotype Strains

Among patients with concomitant distant abscesses (n = 4), the available isolated strains (n = 3) were all of genotype K1 (Table 4). The risk of concomitant distant abscesses was significantly higher in patients infected with genotype K1 strains than in those with non-K1 strains (75% [3 of 4] vs 0% [0 of 6]; $P = .033$). No significant differences were found between the K1 and the non-K1 genotypes in other clinical variables (Supplementary Table 2).

DISCUSSION

This is the first systematic study of monomicrobial KP-NF. It has also presented the largest series to date of patients with this disease. In our study, *K. pneumoniae* (17%) was one of the most common pathogens of monomicrobial NF in northern Taiwan during 1997–2010. The occurrence of monomicrobial KP-NF (11%) was close to that of monomicrobial GAS-NF (12%) among all NF cases. This finding is not isolated. In central Taiwan during 1999–2004, Liu et al found that monomicrobial KP-NF accounted for 22% (13 of 59) of the monomicrobial NF cases and 15% (13 of 87) of all NF cases [19]. In another study, conducted by Chen et al in northern and southern Taiwan during 2002–2005, *K. pneumoniae* (10% [13 of 126]) was as common as GAS among the wound culture–positive monomicrobial NF cases [22]. Hence, after it was first reported in 1996, monomicrobial KP-NF has now become an important entity in cases of NF in Taiwan.

The increased occurrence of *K. pneumoniae* is not restricted to NF. Previous studies in Taiwan jointly indicate that, roughly during 1980–2000, *K. pneumoniae* gradually became a common or predominant pathogen for various diseases, including pyogenic liver abscess [34], lung abscess [35], thoracic empyema [36], brain abscess [37], and bacterial meningitis [38]. Similar changes have also been reported in other countries [39]. The underlying causes of the observed increases remain unclear. Suggested contributing factors include agricultural and medical overuse of amoxicillin and ampicillin since the 1970s [40], the emergence of highly virulent *K. pneumoniae*

Table 2. Monomicrobial *Klebsiella pneumoniae* Necrotizing Fasciitis Cases

Case No.	Age/ Sex	Site(s) of Infection[a]	Sources of *K. pneumoniae* Isolates	Preceding Local Factors[b]	Host Underlying Diseases	Antimicrobial Therapy[c]	Surgical Interventions	Outcome[d]
1	58/M	NF (left hand)	Blood, pus	Intravenous catheter insertion in left hand	DM, LVH, sciatica	Ampicillin/sulbactam, then ticarcillin/ clavulanate plus tobramycin	Debridement	Died from septic shock
2	65/M	NF (left leg, knee, thigh)	Blood, pus	None	DM, steroid use for ITP, HTN	Oxacillin, then cefotaxime plus ampicillin/sulbactam	Fasciotomy, debridement twice, STSG	Alive
3	74/F	NF (left leg, thigh)	Blood, pus	None	DM, nephrotic syndrome, HTN, ICMP, CHF, ischemic stroke	Cefepime plus tobramycin	Fasciotomy, debridement twice	Alive
4	51/M	NF (left foot, leg, thigh)	Pus	None	DM, HBV-related decompensated liver cirrhosis	Oxacillin, then ceftriaxone, then cefepime	Fasciotomy, debridement, BK amputation	Died from hepatic failure
5	56/F	NF (right deep neck)	Blood, pus	Acute tonsillitis	DM, HTN	Ampicillin/sulbactam, then ceftriaxone plus amikacin	Incision, drainage, debridement five times	Alive
6	64/F	NF (right thigh, iliopsoas) with pyomyositis	Blood, pus	Fall with right hip contusion	DM, HTN, hepatitis B with exacerbation	Ampicillin/sulbactam, then ceftriaxone, then imipenem plus amikacin	Debridement seven times, STSG	Alive
7	54/M	NF (right thigh); abscess (brain)	Pus	None	DM, nephrotic syndrome, liver cirrhosis, HTN	Oxacillin plus flomoxef, then flomoxef	Fasciectomy, debridement five times, STSG	Died from septic shock
8	45/M	NF (right forearm, arm, scapular region)	Blood, pus	Heroin injection	DM, alcoholism, chronic pancreatitis, cirrhosis, heroin abuse	Oxacillin plus ciprofloxacin, then imipenem, then ceftriaxone	Debridement four times, STSG	Alive
9	58/M	NF (left thigh, right leg); abscesses (liver, brain)	Blood, pus, liver abscess	None	DM	Oxacillin, then ampicillin/sulbactam plus ciprofloxacin, then ceftriaxone	Fasciotomy, debridement four times, STSG	Alive
10	30/M	NF (left leg); abscess (lung)	Blood, pus, sputum	None	DM	Ceftriaxone, then cefepime	Left lower leg BK amputation	Died from septic shock
11	62/M	NF (right arm, supraclavicular region)	Blood, pus	Right shoulder strain	DM, penile cancer s/p operation	Flomoxef, then imipenem	Fasciectomy	Died from septic shock
12	51/M	NF (left lower leg); abscess (liver: multiple; intra-abdomen: one; right kidney: one)	Blood, pus	None	DM, alcoholism, past history of acute pancreatitis	Amoxicillin/clavulanate, then ceftriaxone	Debridement 4 times, STSG	Alive

13	67/M	NF (right foot, leg, thigh)	Pus	None	DM, CAD s/p CABG, chronic renal insufficiency	Cefpirome	Right thigh amputation, regional fasciectomy	Died from septic shock
14	56/M	NF (left anterior thigh to buttock, back)	Blood, pus	Left hip THR in 1995; traffic accident with left lower leg and chest contusions 1 week before onset of NF	DM, HTN, CAD with MI s/p 6 coronary stents	Ampicillin/sulbactam, then meropenem	Fasciotomy	Died from septic shock
15	65/M	NF (left quadriceps, psoas, iliac) with pyomyositis	Blood, pus	Fall on left thigh	DM, HTN, mitral stenosis, CHF, atrial fibrillation	Ceftriaxone	Fasciectomy, myectomy	Died from septic shock

Abbreviations: BK, below knee; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; HBV, hepatitis B virus; HTN, hypertension; ICMP, ischemic cardiomyopathy; ITP, immune thrombocytopenic purpura; LVH, left ventricular hypertrophy; MI, myocardial infarction; NF, necrotizing fasciitis; op, operation; s/p, status post; STSG, split thickness skin graft; THR, total hip replacement.

[a] Four patients (patients 7, 9, 10, and 12) had concomitant distant abscesses involving the brain, liver, lung, kidney, and/or intra-abdomen. Concomitant liver abscesses were found in 2 patients (patients 9 and 12), among the 11 (of 15) patients who were evaluated for the presence of liver abscesses, using abdominal sonography, computed tomography, or magnetic resonance imaging.

[b] Case 1 was hospital acquired; the remaining 14 cases were community acquired.

[c] Including initial empirical treatment and the definite regimen prescribed after microbiological reports became available.

[d] Of the 15 monomicrobial *K. pneumoniae* NF cases, 7 (47%) died from the infection, and 3 (20%) received BK or AK amputation. For the other 119 NF cases in our series (including polymicrobial, other monomicrobial, and culture-negative cases; Table 1), the risk of infection-related mortality was 37% (44 of 119); limb loss, 24% (28 of 119). Specifically, the risk of mortality and limb loss, respectively, was 42% (14 of 33) and 21% (7 of 33) in polymicrobial NF; 19% (3 of 16) and 25% (4 of 16) in monomicrobial group A *Streptococcus* NF; 45% (5 of 11) and 18% (2 of 11) in monomicrobial methicillin-resistant *Staphylococcus aureus* NF; 25% (2 of 8) and 13% (1 of 8) in monomicrobial methicillin-susceptible *S. aureus* NF; 33% (3 of 9) and 22% (2 of 9) in monomicrobial *Vibrio vulnificus* NF; 83% (5 of 6) and 0% (0 of 6) in monomicrobial *Escherichia coli* NF; 40% (2 of 5) and 20% (1 of 5) in monomicrobial *Aeromonas hydrophila* NF; and 15% (2 of 13) and 31% (4/13) in culture-negative NF.

strain(s) [26], and/or as-yet-unidentified risk factors in the population [39].

Our study shows a consistent trend of more severely compromised host immunity in the monomicrobial KP-NF cases, compared with GAS-NF cases, in terms of diabetes mellitus (100% vs 50%), other immunocompromising conditions (40% vs 25%; statistically nonsignificant), as well as the presence (100% vs 63%) and number (mean, 1.5 vs 0.8) of any underlying immunocompromising conditions. This indicates that compromised host immunity plays a greater role in the pathogenesis of KP-NF than of GAS-NF. Contrasted with other infectious diseases (eg, suppurative infections like endophthalmitis and abscesses in liver or other organs), NF involves the unique feature of extensive fascial necrosis [1]. GAS is well-known for producing proteases and other exotoxins that are capable of destroying tissues in otherwise healthy hosts [1, 41]. Up to 37% of our GAS-NF cases occurred in immunocompetent persons, whereas the KP-NF cases all had underlying immunocompromising conditions. The preponderance of immunocompromised hosts in our monomicrobial KP-NF cases is consistent with prior literature from Taiwan and other countries. On the basis of published reports with detailed case descriptions [7–17], there were a cumulative total of 15 monomicrobial KP-NF cases, of which 12 (80%) had diabetes mellitus, 6 (40%) had other immunocompromising conditions, and 14 (93%) had any underlying immunocompromising conditions. These data, along with our results, suggest that compromised host immunity is an important precipitating factor of monomicrobial KP-NF.

Hematogenous spread (instead of direct subcutaneous invasion via preceding local injury) has been proposed as an alternative pathogenesis mechanism of NF [1]. Monomicrobial KP-NF had a significantly higher occurrence of bacteremia (80% vs 31%), compared with GAS-NF. It also had more cases lacking preceding local factors (53% vs 37%). These indicate the relative importance of hematogenous spread in the pathogenicity of *K. pneumoniae*. In the 8 *K. pneumoniae* cases without preceding local factors, the NF might have resulted from hematogenous spread of the bacteria from a distant septic focus, such as pyogenic liver abscesses [5–7, 10, 14], or from gut bacterial translocation, which is precipitated by liver cirrhosis and/or other immunocompromising conditions [8, 13, 15].

An important finding of this study is that up to 27% of monomicrobial KP-NF cases had concomitant distant abscesses, the risk of which increased with K1 genotype. When NF and distant abscess(es) coexist, it is most likely that one is the primary infection focus, while the other is a secondary complication by bacterial hematogenous spread. Resistance to serum killing is a prerequisite for hematogenous spread. We have previously shown that K1 has the highest level of serum resistance (and hence is the most virulent), followed by K2, or K5/K20/K54,

Table 3. Comparison of Monomicrobial Necrotizing Fasciitis Between Patients Infected With *Klebsiella pneumoniae* and *Streptococcus pyogenes*

Characteristic	*K. pneumoniae* (n = 15)	*S. pyogenes* (n = 16)	*P*
Age, years, mean (range)	57.1 (30–74)	55.8 (22–77)	NS
Male:female ratio	12:3	11:5	NS
Sites of necrotizing fasciitis[a]			
Lower extremities	11 (73)	14 (88)	NS
Upper extremities	3 (20)	1 (6)	NS
Neck or trunk	3 (20)	1 (6)	NS
Preceding local factors	7[b] (47)	10[c] (63)	NS
Local signs on admission			
Local inflammation[d]	15 (100)	16 (100)	…
Crepitation	3 (20)	0 (0)	NS
Bullous lesion	4 (27)	7 (44)	NS
Severity of sepsis syndrome[e]			
Sepsis	15 (100)	16 (100)	…
Sepsis-related hypotension	11 (73)	11 (69)	NS
Sepsis-related organ dysfunction	9 (60)	8 (50)	NS
Intensive care in ICU	13 (87)	11 (69)	NS
Bacteremia[f]	12 (80)	5 (31)	.011[g]
Concomitant distant abscesses	4[h] (27)	0 (0)	.043[g]
Immunocompromising conditions[i]			
Diabetes mellitus[j]	15 (100)	8 (50)	.002[g]
Other	6[k] (40)	4[l] (25)	NS
Any	15 (100)	10 (63)	.018[g]
No., mean (range)	1.5 (1–3)	0.8 (0–2)	.006[g]
Operations, No., mean (range)	2.8 (1–7)	2.8 (2–6)	NS
Outcomes			
Limb loss	3 (20)	4 (25)	NS
Infection-related mortality[m]	7 (47)	3 (19)	NS

Data are No. (%) of patients, unless otherwise indicated.

Abbreviations: ICU, intensive care unit; NS, statistically nonsignificant.

[a] Some patients had >1 site involved.

[b] Intravenous catheter insertion in left hand (n = 1); acute tonsillitis (n = 1); fall with right thigh contusion (n = 1); heroin injection (n = 1); right shoulder strain (n = 1); left total hip replacement in 1995, traffic accident with left lower leg and chest contusions 1 week before onset of necrotizing fasciitis (n = 1); and fall on left thigh (n = 1).

[c] Local injection (n = 1); traffic accident with left femur fracture (n = 1); ankle sprain (n = 1); foot ulcer (n = 1); leg ulcer (n = 1); cutting wound (n = 1); fall (n = 1); leg injury (n = 1); burn injury (n = 1); and intra-uterine device infection with right salpingitis and acute suppurative infection of peritubal soft tissue status post salpingectomy, complicated by postoperative necrotizing fasciitis over right inguinal area and right flank (n = 1).

[d] Defined by the presence of ≥2 of the following signs or symptoms: local pain/tenderness, localized swelling, redness, or heat.

[e] Sepsis, sepsis-related hypotension, and organ dysfunction were defined on the basis of the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus [33].

[f] For all patients in both groups, blood cultures were conducted before initiating antibiotic therapy.

[g] By the Fisher exact test or the Wilcoxon rank sum test.

[h] Brain abscess (n = 1), liver abscess and brain abscess (n = 1), lung abscess (n = 1), and intra-abdominal abscess, right kidney subcapsular abscess, multiple liver abscess (n = 1).

[i] Some patients had >1 condition.

[j] Diabetes mellitus was defined by the presence of 2 independent fasting plasma glucose measurements of ≥126 mg/dL, 1 casual plasma glucose measurement of ≥200 mg/dL, or a previous diagnosis of diabetes mellitus in patients already receiving antidiabetic agents or insulin [26].

[k] Steroid use for immune thrombocytopenic purpura (n = 1), nephrotic syndrome (n = 1), liver cirrhosis (n = 1), nephrotic syndrome and liver cirrhosis (n = 1), alcoholism and liver cirrhosis (n = 1), and alcoholism (n = 1).

[l] Steroid abuse due to bilateral knee osteoarthritis (n = 1), periodic local steroid injection for bilateral knee osteoarthritis (n = 1), nephrotic syndrome (n = 1), and liver cirrhosis (n = 1).

[m] Death was considered related to the infection of *K. pneumoniae* or group A *Streptococcus* if it occurred before resolution of the signs and symptoms or within 14 days of the onset of necrotizing fasciitis, with no evidence of other causes of death.

Table 4. Virulence Gene Profiles of *Klebsiella pneumoniae* Strains Isolated From Patients With Necrotizing Fasciitis

Case No.	Hypermucoviscousity	*cps* Genotype	*rmpA* Copies	Iron-Uptake Systems				Concomitant Distant Abscesses	Mortality
				kfu	*Yersinia* HPI	*iucABCDiutA*	*iroA*		
Strains isolated from patients with monomicrobial *K. pneumoniae* NF[a]									
2	+	K20	ORF KPP020	+	+	+	+	–	No
			ORF KPP302						
3	–	K54	ORF KPP020	–	+	+	+	–	No
			ORF KPP302						
5	+	K54	ORF KPP020	–	+	+	+	–	No
			ORF KPP302						
6	+	K5	ORF KPP020	+	+	+	+	–	No
			ORF KPP302						
9	+	K1	ORF KPP020	+	+	+	+	Liver, brain	No
			ORF KPP302						
10	+	K1	ORF KPP020	+	+	+	+	Lung	Yes
			ORF KPP302						
11	+	K1	ORF KPP020	+	+	+	+	–	Yes
			ORF KPP302						
12	+	K1	ORF KPP020	+	+	+	+	Liver, intra-abdomen, kidney	No
			ORF KPP302						
14	+	K2	ORF KPP020	–	–	+	+	–	Yes
			ORF KPP302						
15	–	K16	ORF KPP020	+	+	+	+	–	Yes
			ORF KPP302						
Strains isolated from patients with polymicrobial *K. pneumoniae* NF[b]									
NA	–	K2	ORF KPP020	–	+	–	–	–	No

Abbreviations: NA, not applicable; –, absent; +, present; NF, necrotizing fasciitis.

[a] Samples were not available in 5 of the total 15 cases because of the following reasons: (1) in 3 cases (No. 4, 7, and 13), blood cultures yielded negative results; (2) in 1 case (No. 1), the sample was collected in 1997 and found to be nonviable by 2008; (3) in 1 case (No. 8), the sample was not collected because it was in the middle of a long Chinese New Year holiday.

[b] Samples were not available in 6 of the total 7 cases, because the blood cultures yielded negative results. For the only one case with available sample, *K. pneumoniae* (extended-spectrum β-lactamase producing) was found in both blood and wound cultures, along with *Bacteroides fragilis* in wound culture.

and then the other genotypes [26]. This predicts a greater risk of concomitant distant abscesses with K1 genotype, as was observed in present study. The current result agrees with and supports our previous findings on the in vitro virulence characteristics of *K. pneumoniae*. Moreover, it parallels and extends our earlier finding of an increased risk for genotype K1 in terms of septic ocular or central nervous system complications from pyogenic liver abscesses [26]. Our results are also consistent with previous case reports of monomicrobial KP-NF with concomitant distant abscess, in which the only case evaluated for capsular serotype was found to be caused by the K1 strain [7].

The higher risk of concomitant distant abscesses in K1 versus non-K1 strains was unlikely to be confounded by diabetes mellitus, underlying immunocompromising conditions, or plasmid-encoded virulence genes, because these factors were all equally and universally distributed between the 2 groups. Further analysis for the effect of K1 genotype was limited by a small sample size of KP-NF cases (n = 15) because of the rare occurrence of NF. To confirm whether K1 is indeed an independent significant predictor of concomitant distant abscesses would require further study with a much larger sample size that enables adjustment for multiple variables. Nevertheless, in our study on *K. pneumoniae* pyogenic liver abscesses (n = 177), multiple logistic regression analyses have confirmed K1 genotype to be an independent risk factor of septic ocular or central nervous system complications (overall risk, 13%; K1 vs non-K1 strains: 19% [19 of 100] vs 5% [4 of 77]; adjusted odds ratio, 4.8 [95% confidence interval, 1.5–15.7], $P = .009$) [26]. Our findings stress the importance of carefully evaluating patients with monomicrobial KP-NF for the existence of concomitant distant abscesses, particularly in cases caused by genotype K1 strains.

Although *K. pneumoniae* isolates from the 14 community-acquired KP-NF cases were universally susceptible to first-generation cephalosporins, these patients were all aggressively treated with a third/fourth-generation cephalosporin or a carbapenem, most likely because of a critical condition and/or concomitant distant abscess(es) [26]. More data are required to determine the optimal antimicrobial treatment for monomicrobial KP-NF.

Despite surgical interventions and appropriate antimicrobial therapy, monomicrobial KP-NF entailed substantial morbidity and mortality risks that were similar to or greater than that in GAS-NF (limb loss, 20% vs 25%; mortality, 47% vs 19%; both statistically nonsignificant). The relatively high mortality among *K. pneumoniae* cases might be attributed to various factors, such as bacterial pathogenicity and/or more severely compromised host immunity [1, 19].

Contrary to the traditional view that monomicrobial KP-NF is rare or unimportant, we found it to be more common than previously assumed and that it has become a common entity in NF in Taiwan. Monomicrobial KP-NF cases are more likely to have underlying immunocompromising conditions and concomitant distant abscesses, both of which require extra caution in diagnosis and treatment. These findings highlight the need to enhance clinical awareness, epidemiological monitoring, and scientific research of this infection, especially in regions where *K. pneumoniae* is more prevalent.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Financial support. This work was supported by National Science Council, Taiwan (NSC-98-2314-B-002-034-MY2) and National Taiwan University Hospital (NTUH-96-A26 and NTUH-97-S-950).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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