Original Article: Cystic Fibrosis?Pediatric & Adult

Title: Elimination of Australian Epidemic Strain (AES1) Pseudomonas Aeruginosa in a Pediatric Cystic Fibrosis Centre[1]

Kevat 0000-0001-9881-6478 0000-0001-9881-6478 AC (MBBS, MMed) [a,b,c], Carzino 0000-0003-2791-6580 0000-0003-2791-6580 R (BBiolSc) [a,b], Massie J (MBBS, PhD) [a,b,c], Harrison J (MBChB) [a,b,c], Griffiths A (MBBS, BMedSci) [a,b].

(a) Department of Respiratory & Sleep Medicine, Royal Children's Hospital, 50 Flemington Rd, Parkville, Melbourne, Victoria, Australia 3052. [Primary Institution]

(b) Murdoch Childrens Research Institute, 50 Flemington Rd, Parkville, Melbourne, Victoria, Australia 3052.

(c) Department of Paediatrics, University of Melbourne, Parkville, Melbourne, Victoria, Australia 3010.

Correspondence to:

Dr Ajay C Kevat

Department of Respiratory & Sleep Medicine

Royal Children's Hospital

50 Flemington Road

Parkville, VIC Australia 3052

Email: ajay.kevat3@rch.org.au

Telephone: +61 3 9345 5818

Facsimile: +61 3 9345 9154

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Abbreviated Title: Elimination of AES1 Pseudomonas from Pediatric CF Centre

Summary / Abstract

Introduction: In this cohort study spanning an eighteen-year period, we evaluated the prevalence and associated mortality rate of epidemic strains of pseudomonas aeruginosa (PsA), especially Australian Epidemic Strain Type 1 (AES1), in a pediatric cystic fibrosis centre practising cohort segregation and early PsA eradication.

Methods: Cohort segregation was introduced in January 2000. PsA clonal strain was determined by pulse-field-gel-electrophoresis at the time of routine collection of airway specimens. Children with PsA underwent eradication treatment with antipseudomonal antibiotics over 2-3 months. We analysed changes in prevalence and mortality from 1999 - 2016.

Results: The prevalence of AES1 declined from 69 (20%) in 1999 to 16 (5.4%) in 2006, to 1 (0.4%) in 2016. The prevalence of PsA overall diminished less over the same period, from 128 (37%) patients in 1999 to 57 (23%) in 2016. New acquisition of AES1 became less common over time, with no new cases identified from 2011. Those who contracted AES1 had a greater risk of death than those who did not (Odds Ratio 4.9, 95% CI 2.5-9.6). Patients with other AES PsA types were uncommon (AES2 n=5, AES5 n=2, AES14 n=3, AES19 n=1).

Conclusions: Cohort segregation was associated with reduction in AES1 prevalence ascertained by pulse-field-gel-electrophoresis surveillance for patients in a single large pediatric cystic fibrosis centre. Other alterations in practice such as early eradication treatment may also have contributed to reduced PsA prevalence. These factors combined with the transition of chronically infected patients over time to adult centres has eliminated AES1 from our clinic, with an accompanying mortality decrease.

1. Introduction

Pseudomonas aeruginosa (PsA) pulmonary infections in patients with cystic fibrosis (CF) adversely affect lung function and cause respiratory deterioration[1,2]. Several PsA epidemic strains have been identified which are associated with an accelerated decline in lung function, increased healthcare requirements, and a greater risk of death or lung transplantation[3,4,5]. In particular, Australian Epidemic Strain Type 1 (AES1) is highly transmissible and linked to increased morbidity and mortality in children[6,7,8]. An earlier study showed decreasing AES1 infection rates in our single centre cohort of patients over a period of years[9], with a low prevalence of other epidemic PsA strains demonstrated[7]. Infection control practices in our centre have changed considerably over time. In this study we aimed to evaluate changes in prevalence of multiple epidemic PsA strains in our pediatric CF centre practising cohort segregation and early eradication over a longer, eighteen-year period. We also reviewed mortality associated with AES1 infection.

2. Materials and Methods

2.1 Data collection and analysis

Expectorated sputum or cough swab samples were routinely collected at least four times per year from each patient with CF. These formed the vast majority of airway samples analysed, but also included were bronchoalveolar lavage (BAL) samples, largely from those who at the time were less than six years old and were enrolled in a randomised controlled trial of BAL-guided therapy (1999 - 2005) or the AREST CF programme (2006 - 2016) which included BAL after diagnosis and annually[10,11].

Samples were plated onto selective culture media using standard techniques. AES1 clonal strain was determined by pulse-field-gel-electrophoresis (PFGE) performed on PsA-positive airway specimen cultures from 1999 onward; for each patient with PsA infection, at least one sample per year was tested using PFGE, using prespecified standardised interpretation criteria[12]. The presence of other Australian Epidemic Strains (AES) was determined using data obtained from enterobacterial repetitive intergenic consensus-PCR (ERIC). This was performed on samples obtained from our cohort from 2008 to 2013 which were also used in a study investigating sharing of genotypes amongst Australian CF centres[7]. All data were stored in a secure electronic database and analysed using

statistical software (Microsoft Excel ® 2016). For each calendar year, the number of patients with and prevalence of PsA infection (including subdivision by relevant strains) was calculated. For those isolating the AES1 strain from airway culture, the number and proportion of initial versus repeat positive patients was determined for each year. Patient mortality, with linkage to infecting organism, was extracted and presented by year of death. Across cohorts and years, longitudinal and comparison analyses were conducted.

2.2 Interventions

During the period of study, children with PsA identified underwent eradication treatment using anti-pseudomonal antibiotic administration. Although exact antibiotic regimens varied, for inpatients they were comprised of two weeks of intravenous therapy using two drugs (usually tobramycin and one of ticarcillin with clavulanate, ceftazidime or piperacillin with tazobactam) followed by 2-3 months of outpatient inhaled and/or oral therapy. Usual outpatient medications for this purpose were nebulised tobramycin and/or oral ciprofloxacin. Rarely, for example in the setting of known allergy, colistin was utilised instead of tobramycin. Prior to the period of study, eradication treatment for PsA was not routinely pursued.

From January 2000 onward, children with CF were separated into cohorts of those infected with *Burkholderia cepacia*, Multi-resistant *Staphylococcus aureus*, AES1, non-AES1 PsA and other patients, based on sputum sample microbiology. Prior to cohort segregation, hospital spaces such as playrooms, inpatient rooms with multiple beds and outpatient waiting rooms could be occupied by multiple children with CF at the same time, regardless of infecting organism. Children with CF also attended communal camps. Following cohorting, within hospital environments segregated patients were kept in separate sections/rooms, attended physiotherapy sessions and lung function testing at different times, and did not use communal spaces such as outpatient waiting rooms, playrooms or the hospital school together (with the exception of siblings). Outside the hospital, camps were no longer conducted, and those with CF were discouraged from socialising and sharing classrooms with each other; information regarding this was provided to schools.

Other infection control methods also evolved over the study period. Perhaps the most significant of these was the publication in 2012 of a comprehensive national guideline for infection prevention in CF care in Australia[13]; prior to this suggestions for infection prevention and control published by The UK Cystic Fibrosis Trust Infection Control Group[14] were already being followed at our center. From 2003-2005, a hospital-wide quality improvement initiative to improve hand hygiene was run, and in 2006 there was a change in handwashing solution[9]. In 2007 our hospital joined a statewide hand hygiene project ensuring thrice-yearly audits of this aspect of infection prevention[15]. Moving to a newly constructed hospital facility in 2011 allowed for the provision of single rooms for all respiratory inpatients, and immediate allocation of a single outpatient room which children with CF entered on their arrival to clinic, minimising use of shared outpatient space. In the new hospital, the multidisciplinary care team rotated between patients in their individual rooms rather than the patient changing rooms as was occurring prior to this. In January 2016 a policy of patient mask-wearing whilst outside their clinic/inpatient room to reduce droplet-borne infection spread[16] for all children with CF in the hospital was introduced. These measures were generally well-accepted by staff, patients and families[17].

2.3 Ethics

The study was approved by the Royal Children's Hospital Human Research Ethics Committee (HREC Reference Number: 37093). All procedures performed were in accordance with the ethical standards of this committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. Results

All samples were obtained from 1999-2016 from CF patients at our centre, which cared for an average of 294 (range 266 - 344) patients each year over this time (with patients who left the clinic during the year included in these figures). Findings were analysed from a total of 1338 PsA-positive samples tested using PFGE, 398 of which were also tested from 2008-13 using ERIC (Table 1).

The total number and cohort proportion of children with AES1 positive samples decreased from 69 (20%) in 1999 to 16 (5.4%) in 2006 (Risk Difference 15%, 95% CI 10 - 20), and then continued to decline steadily to 1 (0.4%) in 2016, reaching zero in 2017 (Figure 1). The prevalence of PsA overall diminished at a proportionally slower rate over the same time period, from 128 (37%) patients having a positive airway sample in 1999 to 57 (23%) in 2016 (Risk Difference 15%, 95% CI 7 - 22).

First occurrence of AES1 in a patient was infrequent after 2005 (1 patient in 2007, 2 in 2010 and 1 in 2011). The mean age of patients with AES1 progressively increased from 13.8 years to 18.3 years over the eighteen-year period, whereas there was no upward age trend for patients returning a non-AES1 PsA sample (Figure 2).

Of children with any AES (i.e. AES1, 2, 5, 14 and 19), 48% were female. ERIC results for AES detection were almost perfectly concordant with those returned by PFGE (Simple Agreement >99%, Cohen Kappa 0.98). Eleven patients were found to have non-AES1 strains of PsA known to be shared across CF centres, AES2 (5 patients) being the most common of these (Table 2).

The overall death rate declined from 9/year in 1999 to 1/year in 2013 (Risk difference 2.2%, 95% CI 0.03 – 4.5); 56% of CF-related deaths occurred in the first three years of the time period studied (Figure 3), with no deaths from 2014-2016. Those who died over the time period studied (39 patients) were much more likely to have had a positive AES1 sample in the year of / prior to their death (23 patients) compared to a non-epidemic PsA strain (9 patients). A smaller proportion of patients died without having PsA identified (6 patients, 1 who was chronically infected with *Burkholderia cepacia*). A single patient died carrying a non-AES1 strain of epidemic PsA; in this case, AES2. Those who contracted AES1 had a much greater risk of death than those who did not (Odds Ratio 4.9, 95% CI 2.5 - 9.6).

4. Discussion

Following a series of untimely deaths in children under five years of age in our cohort[6], our epidemiological investigation using PFGE and ERIC techniques demonstrated an outbreak of AES1

followed by a dramatic decline in AES1 rates and associated mortality from 2000 onwards, coinciding with the introduction of patient cohorting and early PsA eradication regimens. This provides evidence that these practices can prevent spread of epidemic PsA[18,19,20]. Over the time period studied, mortality in our clinic was predominantly associated with AES1, with other epidemic strains of PsA only detected sporadically and in low numbers in our clinic.

The steady decline in prevalence of AES1 extending over several years is largely due to the transition of patients to adult care centres (in combination with deaths). Although data do not permit accurate differentiation between chronic and recurrent PsA infection states, the increasing age of those with AES1 isolates combined with the low rate of new first AES1 occurrences over time delineates the passage of a chronically infected cohort of patients who have over the years transitioned to adult centres without having AES1 eliminated[21]. Our final patient with AES1 transferred to an adult centre in early 2017, eliminating this organism from our clinic. In another Australian centre however, an AES1 infection rate of 38% has been documented, demonstrating the persistent nature of the infection in individuals and cohorts[21].

The introduction of infection control measures including cohorting was designed to interrupt hospital-based spread of epidemic organisms, and correlated with a sudden decline in the number of new acquisitions of AES1. The decrease in non-AES1 PsA was much less dramatic because these organisms are likely acquired from environmental sources[22], and could be explained by advances in CF care over time, and/or implementation of early PsA eradication which in other centres has been shown to reduce the prevalence of this organism[23]. Quality improvement initiatives to strengthen contact precautions have also demonstrated correlation with reduction in PsA infection[24]. In our hospital, education and audit programs to reinforce safe patient contact, hygiene and infection control practices were enacted over the study time period[25], although their effect on PsA transmission was not specifically evaluated. Despite all of these efforts, late first acquisition of AES1 (i.e. years after establishment of cohorting and eradication practice) did occur in a small number of patients. This may

have been contributed to by a breakdown in stringency of infection control practice over time, or acquisition of AES1 outside the hospital from environmental or person-to-person transmission.

Over the time period studied, a reduction in mortality was achieved in our clinic. Because mortality occurred almost exclusively due to pulmonary causes and the majority of deaths were in patients infected with AES1 which is known to cause pulmonary demise[6,21], it is probable that specific measures introduced to curtail epidemic PsA had a major impact on preventing deaths from infection due to this virulent organism. It is important to note however that other practice changes in CF care have also occurred since 1999. The reduced mortality and improved quality of life seen across many centres for those with CF over this period is likely due to varied advancements including multidisciplinary care and coordination, a focus on comprehensively managing complicating comorbidities such as diabetes and undernutrition, and the implementation of new medical therapies[26].

Our study has some limitations. Data from ERIC-tested samples spans five years, not the eighteen covered by PFGE testing. However, discordant results between these two methods were <1%, consistent with other research comparing the two methodologies in PsA strain typing[27]. Another limitation is that multi-locus sequence typing (MLST) was not employed, although it has been noted that this is a technique perhaps better suited for long-term PsA surveillance[28]. Nevertheless, ongoing low mortality rates, very high rates of concordance between MLST and PFGE and the fact that PFGE is suited to outbreak detection involving related isolates[27] provides reassurance that PsA strains with high transmissibility and morbidity are unlikely to be spreading undetected in this centre.

Additionally, multiple changes to infection control practices were made in our centre. It is difficult to conclude which is of most benefit in preventing epidemic PsA acquisition. Therefore, it would be prudent to continue using a multi-pronged approach for infection management and prevention, with cohort segregation, early PsA eradication, ongoing surveillance for organism outbreaks, strict hygiene practices, and education for patients, families and staff all being employed to protect the health of those with CF.

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Image Legends

Figure 1: Prevalence of AES1 and incidence of new AES1 isolation in a single Australian pediatric cystic fibrosis care centre.

Figure 2: Mean age of patients at time of isolating AES1 and Non-AES1 Pseudomonas aeruginosa from an airway sample over an eighteen year period in a single Australian pediatric cystic fibrosis centre.

Figure 3: Cystic fibrosis related deaths by year and recent airway isolate results from 1999-2016 in a single Australian pediatric care centre.

Year	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
# Total patients	344	322	327	306	303	301	313	296	295	298	291	295	290	273	266	244	259	253
PsA + (% of #)	128 (37)	73 (23)	105 (32)	106 (35)	87 (29)	77 (26)	85 (27)	82 (28)	66 (22)	61 (20)	63 (22)	74 (25)	52 (18)	68 (25)	48 (18)	60 (25)	45 (18)	56 (23)
AES1 (% of #)	69 (20)	39 (12)	50 (15)	46 (15)	38 (13)	28 (9)	31 (10)	16 (5)	11 (4)	11 (4)	7 (2)	8 (3)	7 (2)	6 (2)	5 (2)	2 (<1)	1 (<1)	1 (<1)

Table 1: Prevalence of any Pseudomonas aeruginosa (PsA) and Australian Epidemic Strain 1 Pseudomonas (AES1) over eighteen years in a single Australian pediatric cystic fibrosis care centre.

Original format version:

Year	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
# Total patients	344	322	327	306	303	301	313	296	295	298	291	295	290	273	266	244	259	253
PsA + (% of #)	128 (37)	73 (23)	105 (32)	106 (35)	87 (29)	77 (26)	85 (27)	82 (28)	66 (22)	61 (20)	63 (22)	74 (25)	52 (18)	68 (25)	48 (18)	60 (25)	45 (18)	56 (23)
AES1 (% of #)	69 (20)	39 (12)	50 (15)	46 (15)	38 (13)	28 (9)	31 (10)	16 (5)	11 (4)	11 (4)	7 (2)	8 (3)	7 (2)	6 (2)	5 (2)	2 (<1)	1 (<1)	1 (<1)

Table 1: Prevalence of any Pseudomonas aeruginosa (PsA) and Australian Epidemic Strain 1 Pseudomonas (AES1) over eighteen years in a single Australian pediatric cystic fibrosis care centre.

	2008	2009	2010	2011	2012	2013	*Total # patients*
AES2: total (new) patient isolates	1 (1)	1 (1)	0 (0)	1 (1)	3 (2)	0 (0)	(5)
AES5: total (new) patient isolates	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	(2)
AES14: total (new) patient isolates	2 (2)	3 (1)	2 (0)	1 (0)	1 (0)	1 (0)	(3)

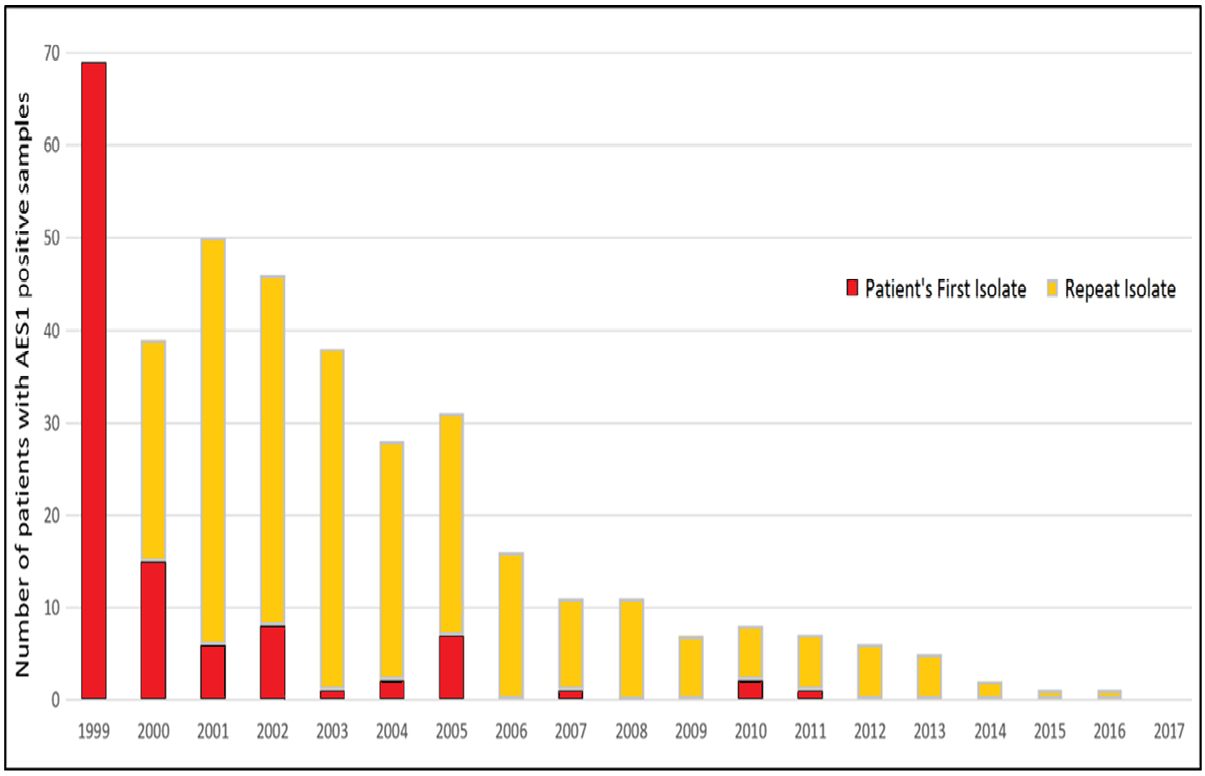
AES19: total (new) patient isolates	1 (1)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	(1)
Total	5 (5)	5 (2)	4 (1)	3 (1)	5 (2)	2 (0)	(11)

Table 2: Number of patients with Australian Epidemic Strain Pseudomonas (non-AES1 types) detected by ERIC sampling from 2008-13 in a single Australian pediatric cystic fibrosis centre.

Original format version:

	2008	2009	2010	2011	2012	2013	*Total # patients*
AES2: total (new) patient isolates	1 (1)	1 (1)	0 (0)	1 (1)	3 (2)	0 (0)	(5)
AES5: total (new) patient isolates	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	(2)
AES14: total (new) patient isolates	2 (2)	3 (1)	2 (0)	1 (0)	1 (0)	1 (0)	(3)
AES19: total (new) patient isolates	1 (1)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	(1)
Total	5 (5)	5 (2)	4 (1)	3 (1)	5 (2)	2 (0)	(11)

Table 2: Number of patients with Australian Epidemic Strain Pseudomonas (non-AES1 types) detected by ERIC sampling from 2008-13 in a single Australian pediatric cystic fibrosis centre.



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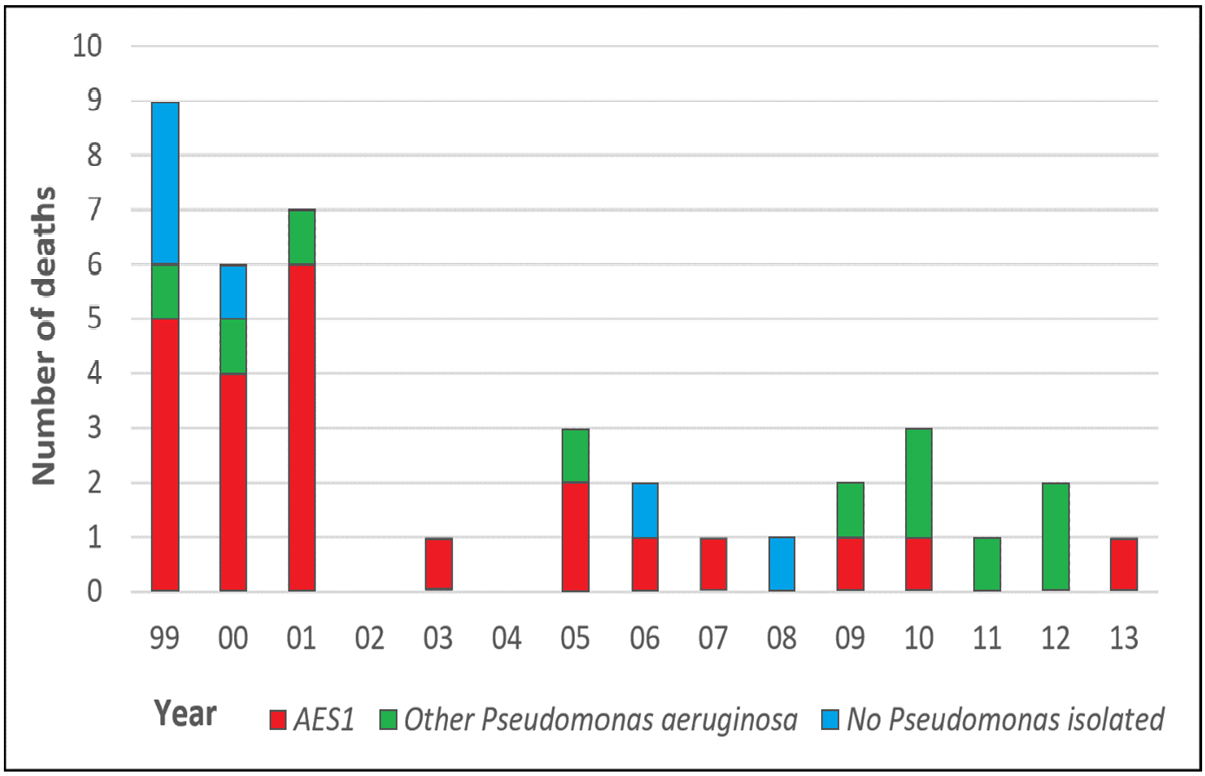

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Author/s:
Kevat, A; Carzino, R; Massie, J; Harrison, J; Griffiths, AL

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